The New England
Journal of Medicine

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Volume 250 APRIL 1, 1954 Number 13

MORPHOLOGIC AND HEMODYNAMIC CHANGES IN THE SMALLER BLOOD VESSELS IN DIABETES MELLITUS*

I. Considerations Based on the Literature

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SINCE the most serious problem in diabetes mellitus today is the associated vascular degeneration, a proper understanding of the pathology and pathogenesis of these changes is essential. This is particularly true in the light of the recent report that the retinal changes in diabetes may be reversible,[1] giving hope that a rational therapy may be found if causative factors are known. There is rapidly accumulating evidence that the lesions in the smaller blood vessels are most characteristic of the generalized abnormality of the vessel walls. The structural integrity of the walls of the larger vessels is dependent on the function of the vasa vasorum, and the generalized vascular disease therefore might show in part the same underlying pathology.

It has been demonstrated that the capillaries are basically involved and have a characteristic morphology in two common manifestations of the vascular disease: retinopathy and intercapillary glomerulosclerosis. Since the capillary changes can precede sclerosis in other parts of the vascular system, the capillary lesion may represent the initial degenerative process. These features point out the necessity of obtaining all possible information about the capillaries in diabetes. This review summarizes some of the present knowledge regarding the changes in the smaller blood vessels and simultaneous hemodynamic variations.

Too frequently, the importance of the capillaries in vascular pathophysiology has not been appreciated. This fact, combined with the technical difficulties inherent in study of the capillaries, has severely limited the accumulation of data. The information about the capillaries and the smaller vessels has been obtained from two distinct modes of investigation: a pathoanatomic study of flat preparations or of serial sections of tissue, and a direct study of the vascular system in living persons by observation of the retina, of the conjunctiva and of the fingernail bed.

The functional capillary wall consists, first, of a single layer of endothelial cells bound together by intercellular cement substance and, secondly, of a pericapillary sheet surrounding the capillary. Although in many tissues the pericapillary sheet cannot be differentiated from the diffuse-staining ground substance of the connective tissue, in certain organs the sheathing is well defined and is called the basement membrane. The vascular tree of the retina and the capillaries of the renal glomeruli and of the islands of Langerhans have such a distinct basement membrane. The exact nature of the basement membrane has not been established, but it contains an acid mucopolysaccharide since it reacts brilliantly with Hotchkiss–McManus stain. The basement membrane is closely related to the ground substance of the connective tissue since both have similar staining properties and both react to the agents affecting the connective-tissue matrix.[2, 3] The endothelial cells play an important part, apparently producing both the intercellular cement substance and the similarly acting basement membrane; the chemical stability and reactivity of these substances control the permeability of the blood capillary.[4]

The capillary circulating blood provides for an optimal composition of the fluids to satisfy the varying metabolic demands of the tissue cells. In the mesoappendix of the rat a main factor determining the blood flow from the arteriole to the venule is the phasic activity of the precapillary sphincters (vasomotion). Its activity is modified by the status of the chemical composition of its fluid environment and innervation. Activated vasomotion causes a rapid exchange of constituents between the vascular and tissue-fluid compartments. Atony of the capillary smooth muscle leads to stagnation of the tissue-fluid circulation. Epinephrine and adrenocortical steroids promote sphincter vasomotion, whereas adrenergic blocking agents inhibit vasomotion.[4] This may be of importance in relation to

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Aided by grants from Nordisk Insulin Fond, Denmark, the Proctor Fund of Harvard Medical School and the Diabetic Fund of Boston.
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diabetes, since there is evidence that this condition is associated with a functional imbalance of the adrenal cortex.[5-7]

In most tissues new capillary formation can easily take place if stimulus to growth is present. It is to be expected that in such tissues capillary degeneration will not give rise to symptoms. However, in the kidney the glomerular capillaries cannot be replaced because they are associated with other structures in a complicated excretory apparatus. An extensive capillary replacement will damage the highly differentiated function of certain tissues (such as the retina and nerves). Structures like the inner nuclear layer of the retina,[8] the glomeruli of the kidney[9] and the islet cell of the pancreas,[10] in which the capillary bed forms the only vascular component, are extremely vulnerable to capillary degeneration. Although the capillary degeneration might be general these tissues would be more highly affected. In diabetes, as is well known, the "complications" appearing after long duration of the condition are those affecting the kidney and the retina. Not recognized until recently is the similarity of the changes that have taken place in these and other tissues. Some of these similarities, as well as differences, and their potential bearing on the basic physiology and pathology of the disease are discussed below.

Changes in Smaller Blood Vessels

Morphologic Changes in Capillaries

Retina. The recent studies of flat preparations of the whole retina by special staining and injection technics have yielded valuable information about the capillary pathology in diabetes.[11, 12] Attention has recently been called to the presence of capillary microaneurysms in the retina. Their appearance was briefly described by MacKenzie[13] in 1877 and by Parsons[14] in 1905. However, when insulin was introduced the observations of these authors were forgotten. In 1943 Ballantyne and Loewenstein[15] rediscovered the so-called "punctate hemorrhages," which they showed to be capillary microaneurysms.

In diabetic patients true capillary microaneurysms may be found in considerable number on the venous part of the capillaries and are particularly aggregated in the posterior polar region of the retina.[15] This has been confirmed and the observation made that they are usually observed only in the two-dimensional, close-knit network of the capillaries of the inner nuclear layer.[16] The size of the microaneurysms is variable, often only 20 to 30 microns in diameter, and they are therefore not generally visible with the use of an ophthalmoscope. Some microaneurysms, when colored by Hotchkiss–McManus stain, have markedly thickened walls containing a component that stains like the basement membrane.[17] Microaneurysms may or may not be associated with the thickening of the basement membrane. There seems to be no doubt about the importance of the capillary lesion in the picture of diabetic retinopathy since flame-shaped hemorrhages and exudates surround the aneurysms. Because the retina is not routinely examined by the pathologist in cases of diabetes, knowledge regarding the occurrence of aneurysms in relation to the duration of the diabetic condition is lacking.

Other capillary changes are found in the retina, but have not been given enough attention. A normal, injected retina shows a regular capillary pattern. An early change in diabetes is a complete distortion of the normal arrangement, with elongation, angular course and subsequent looping of the capillaries,[11, 18] often resulting in proliferation of new vessels. Serial sections of the retina frequently reveal dilatation of the capillaries and hyalinization of the wall.[19] Capillaries can proliferate into the vitreous body in a formation of connective tissue from the disk (retinitis proliferans). Klien[20] believes that in diabetes, as in other diseases associated with vascular degeneration leading to extensive anastomoses, the primary course is new vessel formation. Since newly formed vessels, which often develop from the venous part of the capillary or venules and pass to the venules, are more permeable than normal capillaries, they are more likely to produce hemorrhages.[21] Hemorrhages are often associated with and aggravate retinitis proliferans. A rare primary cause of retinitis proliferans in diabetes is a massive hemorrhage from a varicose vein.[22]

Kidney. The capillaries of the glomeruli of the kidney in diabetes have been extensively studied since the description of the so-called intercapillary glomerulosclerosis by Kimmelstiel and Wilson[23] in 1936. The importance of the morphologic changes in the capillaries of the glomeruli has been stressed by numerous authors.[23-25] The changes consist of proliferation and hyalinization of the capillary wall. One or more of the peripheral parts of the capillaries are almost constantly dilated. Allen[24] emphasized the fact that the capillaries encircling the large nodular hyaline deposits are always greatly dilated and congested, with evidence of stasis. This dilatation of the capillaries, which is characteristic of the Kimmelstiel–Wilson lesion, has been described by some authors as microaneurysm-like.[11, 12] Although it was originally thought that the hyalinized laminated masses were located in an "intercapillary space" Rinehart et al.[26] recently showed conclusively by special staining technics that the glomerular alteration in diabetes is a striking thickening of the endothelial element of the basement membrane. Laipply, Eitzen and Dutra[27] and others[28,29] have described the first stage of glomerulosclerosis as a diffuse hyalinization between the capillary tufts. In the later stages this form can be seen together with the characteristic hyaline nodules. Few authors have

found it possible to distinguish these lesions from those produced by nephritis and arteriosclerosis because of the diffuse character of the hyalinization combined with the absence of features characteristic of the nondiabetic glomerular lesion.[30]

The development of the Kimmelstiel–Wilson lesion is not caused solely by arteriosclerosis in the renal vessels since either sclerosis or the lesion may be found in the absence of the other condition.[27] Zins[30] found that 82 per cent of 50 patients with an average duration of diabetes of six years had capillary changes if his figures took into account the stage of diffuse hyalinization, which is not included in statistics on the Kimmelstiel–Wilson lesion. He further stated that theoretically it might be possible to find this capillary lesion in 100 per cent of diabetic patients if a more thorough examination of many sections from different parts of the kidney were performed.

Other tissues. Theoretical consideration of the possible changes in the capillaries and in the tissue of the islands of Langerhans shows them to be similar to those occurring in the retina and the glomeruli of the kidney since the circulation of these three organs is somewhat similar. Opie[31] first described the hyaline changes occurring in the islets of the pancreas. The investigation of Hartroft[32] has supported the suggestion that the pathogenesis of hyalinization in the islands of Langerhans is similar to that taking place in the glomeruli and in the retina. A study of pancreatic tissues gave evidence of changes in the islets or the basement membrane of the capillaries in 41 of 46 cases of diabetes.

Further evidence for the extensiveness of the capillary lesion in diabetes was presented by Müller,[33] Weiss[34] and Jürgensen,[35] all of whom agreed that changes characterized by a distention of the midloop and venous part of the capillaries or a bizarre dilated deformation of the capillary tufts occur in the fingernail bed. The finding was recently confirmed by Frehner,[36] although this work was also done on a small series of diabetic subjects. A further investigation of these changes should now be made on a much larger series of cases, studied in greater detail. Zeller[37] briefly mentioned dilatation of the venous part of the capillaries in the conjunctiva. Using histologic technics Ashton[16] examined a number of tissues (the conjunctiva, the iris, the pleura, the omentum, the meninges and so forth) but was unable to find any capillary microaneurysms. Recently, Friedenwald[17] studied the conjunctival vessels in 60 cases of diabetic retinopathy. In only 1 was a single capillary aneurysm found. He stated that "since such aneurysms are occasionally seen in non-diabetics, no significance is to be attached to these findings." On the other hand, McCulloch and Pashby[38] claimed that microaneurysms in the conjunctival vessels occur in a much higher number.

Functional Changes in Capillaries

During the last few years there has been accumulating evidence that the membrane function of the capillaries is disturbed early in the diabetic state. It is well known that the capillary fragility is often increased.[39] Barnes[40] found in a series of 220 diabetic patients that the capillary-fragility index was higher in 85 per cent of those with retinopathy and up to 55 per cent of those without retinopathy or hypertension. Rodrigues and Root[41] reported that the increased fragility of the capillaries was correlated with the duration of the disease. The pathogenesis of the increased capillary fragility is unknown, and more attention must be given to this disturbance. The phenomenon seems related to changes in the physicochemical state of the basement membrane. Experimentally, it has been shown that pericapillary application of hyaluronidase will produce increased fragility.[4]

Frehner,[36] using the method of Amsler and Huber[42] of measuring fluorescein diffusion through the blood-aqueous barrier, observed that 48 per cent of a series of 25 patients with uncomplicated diabetes showed significantly increased permeability. Correlation was found between the degree of permeability and the age of the patient and the duration of the disease. In the same group of patients an elevated Donaggio reaction (urinary excretion of protective colloid) was noted in 48 per cent. Amsler[43] reported that inulin clearance without clinical evidence of complications was significantly elevated in 50 per cent and the para-aminohippurate clearance decreased in 70 per cent of diabetic patients investigated. Even though such a finding is difficult to explain it may be indicative of a disturbance in the permeability of the glomerular tufts.

Changes in Arterioles and Venules

Arterioles. Arteriolar sclerosis is a common observation in diabetes. The lesion consists of a subintimal hyaline thickening, with narrowing of the lumen and replacement of part of the muscular layer. Bell[28] emphasizes the thick homogeneous hyaline deposit in the arterioles as being strong presumptive evidence of diabetes.

"Arteriosclerosis" in the retinal vessels is often associated with retinopathy. Waite and Beetham[44] described arteriosclerosis of the retinal vessels in about 75 per cent of the 2893 cases of diabetes reported. They noted an over-all correlation between the grade of sclerosis and the duration of the disease, but pointed out that there were patients in whom no such correlation existed. They further stressed the point that these vessel changes did not explain the diabetic retinopathy:

> To explain the source of these deep retinal hemorrhages, we should seek more information about the physiology and pathology of the retinal capillaries, about their normal and

abnormal hydrodynamics, about glycogen deposits which are known to affect other ocular tissues, about their normal and abnormal permeability of the capillary walls, about thromboses which may form within them, and about toxins which may affect them adversely. Until this knowledge is forthcoming, either from clinical studies or from the study of laboratory animals, we can form no valid opinion about the source of deep retinal hemorrhages in diabetics.

Although this paper was written in 1935 the statement in general holds true, since the problems outlined are fundamental and until recently little or no work was carried out on these basic aspects.

Arteriolar sclerosis of the renal vessels is also frequently associated with glomerulosclerosis, and many authors[25, 28, 45] consider the pathogenesis of this lesion to be related to severe arteriolar degeneration. Siegal and Allen,[46] however, indicated that the lesion was not secondary to marked nephrosclerosis because glomerulosclerosis could be present in cases of diabetes without severe renal arteriolar sclerosis. This view has been supported by the investigations of Laipply et al.,[27] Porter and Walker[47] and Friedenwald.[25]

Venules. There is increasing evidence of the extensiveness of the sclerotic lesion in the venules of diabetic patients. Many consider the venous changes important in the pathogenesis of diabetic retinopathy. Ophthalmoscopic study has revealed a congestion of the venules with the appearance of venous stasis as an early change in the vascular pathology. This finding has been emphasized by many authors.[49-51] Different types of involvement can be observed: venous engorgement, dilatations and fusiform swelling concomitant with increased tortuosities of the venules. Pathological examination shows a process of phlebosclerosis as well as endothelial proliferation with variable blocking of the lumen.[19, 52] Gibson[53] believes that capillary microaneurysms are not to be regarded as a primary independent event, but may be secondary to this venous occlusive phenomenon due to endothelial proliferation.

It is evident from this discussion of changes in the smaller blood vessels that the fundamental pathology is basically one of the endothelial cell and the basement membrane. The morphologic changes in the smaller blood vessels can be seen from the proliferation of the endothelium and the accumulation of hyaline nodules and hyaline thickening in the kidney glomeruli and in the capillary basement membrane in the retina. The initial morphologic changes in the capillaries are associated with a functional disturbance of the important blood-tissue barrier since there is an increased fragility and possibly an increased permeability of the vessels.

Pathogenesis of Capillary Changes

The problem of the pathogenesis of the widespread capillary hyalinization in diabetes cannot be solved with information at present available. Most hypotheses concerning the pathogenesis can probably be incorporated in the following:

An impairment of the blood circulation in the terminal peripheral vascular system leading to prolonged suboxidation and subnutrition of the endothelium.[26, 54]

A metabolic disorder of the simple polysaccharides (glycogen) or complex polysaccharides (mucopolysaccharides) that involves the basement membrane of the capillaries and the ground substance of connective tissue.[17, 55, 56]

The microaneurysms in the retinal capillaries of diabetic patients are characteristic in number, location and size but are not a specific lesion of the disease. Ashton[54] found them in subjects with long-standing fatal diseases as well as in glaucoma and other eye disorders. Becker and Post[57] produced great numbers of aneurysms in animals by occluding the central retinal vein. Wexler and Branower[58] reported capillary microaneurysms in malignant hypertension. These differ, however, from those seen in diabetes since the microaneurysms were found at the arterial rather than at the venous part of the capillary.

The location of the microaneurysms in the inner nuclear layer suggests a chronic condition of stasis as the cause of such lesions. A possible stasis would logically be produced to a greater degree in the close-knit network of these capillaries, which offer more resistance than those in the superficial plexus of the retina in case of changes of venous circulation.[59] Evidence of venous stasis is given by the frequent observation of the congested appearance of the retinal veins and more indirectly by the frequent finding of thrombosis in dilated capillaries and venules in preparations of the retina.[60] The venous stasis in diabetes may be related to several factors, including the composition of the circulating blood and the dilatation of the venules.

The state of the circulating blood is a function of the composition of the blood plasma, the number of blood corpuscles and their structure and distribution within the plasma. The stability of the blood cells as a suspension depends on the colloidal constituents of both the cells and the plasma.[61] In general any changes in the normal protein pattern will cause aggregation of the blood cells.[62, 63]

Knisely and his co-workers[64] have described aggregation of the blood cells (sludged blood) in numerous conditions such as infections and neoplastic and metabolic diseases. Ditzel[65] has shown that in 95 per cent of a large group of diabetic patients with retinopathy the blood cells were aggregated and that these aggregates varied greatly in size and rigidity from case to case. According to Knisely et al.[64] the blood cells of healthy persons are not aggregated, and the blood flow through the smaller blood vessels in sections of the bulbar conjunctiva magnified forty-eight to sixty-four times is so rapid

that individual erythrocytes cannot be seen. In diabetes, however, the aggregation of the blood cells is often extensive, and clumps of blood cells appear even in the terminal arterioles, where they may intermittently plug the tip of the arterioles. The rate of flow is slowed to a considerable degree, and settling of the larger aggregates may occur so that "pseudothromboses" are formed, obstructing the lumen of the capillaries and smaller venules.[65] The fact that the aggregation phenomenon is related to protein changes and is present in circulatory disturbances of diabetic patients may explain why there was some indication that retinopathy was benefited by treatment with a high-protein diet,[66-68] which restored the normal blood protein pattern and probably normal blood suspension stability. Also, ACTH and cortisone cause changes in the albumin-globulin ratio and likewise may cause changes in the degree of aggregation of the blood cells.[69-71] Observations on animals indicate that Dicumarol, as well as heparin, affects the physical properties of aggregates so that they do not become attached to the vessel walls as they usually do.[72] This, of course, is of interest from the standpoint of both the etiology and the treatment of the circulatory impairment in the smaller vessels.

Any venular dilatation without concomitant arteriolar dilatation will result in a slowing down of the rate of blood flow. The cause of the venous dilatation in diabetes is not known. Emphasis has been placed on the blocking effect of endothelial proliferation in phlebosclerotic veins. The venous "back pressure" should produce stasis, anoxemia and subsequent endothelial degeneration with aneurysm formation in the capillaries.[53] Elwyn[73] stresses prolonged hyperglycemia as a cause of venous dilatation.

The second possible explanation of the development of hyalinization is strongly supported by Spühler and his co-workers, who in a series of investigations have been interested in the changes of capillary permeability in diabetes. Spühler and Zollinger[55] suggested that the typical characteristics of diabetes were due to membranous changes as seen in the glomerular loops, in the tubules of the kidney, in the retina and generally in the arterioles. Friedenwald,[11] by applying the Hotchkiss–McManus technic to preparations of the kidney and the retina, emphasized the similar staining properties of the hyaline nodules in the glomeruli and the microaneurysms of the retina. He stressed the probability of the same underlying pathogenesis. The Hotchkiss–McManus stain revealed substances containing mucoproteins and suggested a possible metabolic change in these substances in diabetes. Lately, Warren and Le Compte[60] have tried to interpret all the characteristic alterations in diabetes, including the hyalinization of the islands of Langerhans, by metabolic changes in the simple polysaccharide (glycogen) and the more complex form, mucopolysaccharides.

Recently, work on lipid metabolism has indicated the possibility that it is also involved in the degenerative process. Ballantyne[60] has stained flat preparations of the retina for fat and found considerable amounts located in the wall and in the perivascularly situated macrophages. Engelberg, Gofman and Jones,[74] as well as Keiding et al.,[75] have shown a disturbed lipid transport in diabetes, particularly in cases with vascular complications. It is of interest not only that small clusters of fat droplets (chylomicrons) appear in the blood of human beings after the ingestion of a fat meal but also that there is a concomitant tendency of the blood cells to aggregate in vitro into sticky and irregular clumps. Intravenous injections of heparin in cases of marked lipemia cause at the same time a disappearance of chylomicrons and an increase in the buoyancy of the red blood cells.[76]

Conclusions

The capillary changes in diabetes are widespread, occur principally in the venous part and appear to have a common pathology characterized principally by hyalinization. The relation between the metabolic disturbance and the vascular degeneration is unknown.

Since the capillaries show the first and probably the purest form of any vascular abnormality and since it appears that the smaller blood vessels and arterial blood flow in the bulbar conjunctiva are at least representative of the subcutaneous vascular system and its hemodynamics, further investigation of the problem of vascular degeneration may be properly approached through the study of the conjunctival vessels. Such a long-term project has been started and a preliminary report will be presented in the following paper.

I am indebted to Professor C. Holten and Professor K. Lundbaek, Arhus University Medical School, Denmark, for stimulating advice and help with the initial stages of this work, and to Drs. Alexander Marble and Elizabeth F. Tuller for their invaluable help in the preparation of this paper.

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SERUM PHOSPHORUS AND POTASSIUM LEVELS AFTER INTRAVENOUS ADMINISTRATION OF GLUCOSE*

Their Use as Diagnostic Aids in Diabetic and Nondiabetic Subjects with and without Liver Disease

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IT is well known that the concentration of inorganic phosphorus of the blood serum of normal dogs[1-3] and men[4-9] falls after the ingestion or infusion of glucose. In diabetes mellitus this drop is less marked and often prolonged, and at times there is no fall.[9, 10] This has been ascribed to decreased peripheral utilization of glucose due either to pancreatic insufficiency or to insulin antagonists.[9]

Early studies also showed that in normal and diabetic persons insulin enhances the reduction in serum inorganic phosphorus.[4, 5, 8, 11-15] Pollack et al.[3] demonstrated marked participation of phosphate in the utilization of glucose in the hind limb of the dog, little phosphate being taken up by the perfused liver. The work of Bolliger and Hartman[16] also suggested that the major utilization of phosphate was not in the liver. With this as a background, Forsham and Thorn[10] proposed that the inorganic phosphorus curve during the intravenous glucose tolerance test be used to differentiate hyperglycemia caused by diabetes mellitus (peripheral underutilization of glucose) from that due to overproduction of glucose by the liver (hepatic-storage insufficiency). They found that the average maximum fall in serum inorganic phosphorus was 12 per cent in diabetic patients as contrasted with 25 per cent in normal controls. In a group of patients with liver disease the average maximum fall was 37 per cent. However, the data showed a considerable overlap in these three groups, and more recent work by Schneeberg[19] and Volk and Lazarus[9] demonstrated a similar overlap in diabetic and normal persons. This was in agreement with earlier work by McCullagh and Van Alstine.[20] Blatherwick, Bell and Hill[11] found no fall or rise in the oral glucose tolerance test in 3 of 10 normal subjects.

Changes in serum inorganic potassium during intravenous glucose tolerance tests have been studied by Wilson et al.[21, 22] in normal and diabetic persons. In 23 normal subjects a maximum potassium fall of 0.1 to 0.3 milliequiv. per liter occurred, only 2 exceeding 0.3 milliequiv. The 22 diabetic patients were divided into three groups: 9 not requiring insulin and having no liver disease had a mean maximum reduction of potassium of 0.57 milliequiv. per liter; 6 taking insulin and without liver disease had a drop of 0.1 milliequiv.; and 7 with both diabetes and liver disease showed a fall of 0.19 milliequiv. It was concluded that the larger decreases in potassium were associated with either insulin deficiency or insulin excess and further postulated that the reduction in serum potassium during the test might be the earliest detectable abnormality of relative or absolute insulin lack. Groen et al.,[23] however, reported much higher falls in inorganic potassium in nondiabetic patients given prolonged infusions of glucose, although in some cases there was little or no drop.

The purpose of this report is to present blood sugar, serum inorganic phosphorus and potassium values obtained during glucose tolerance tests in nondiabetic persons and in patients with slight abnormalities of carbohydrate metabolism. Some subjects from both groups had evidence of liver damage. Patients with early, incipient or "mild" diabetes were selected because it is in this group that differences of opinion regarding diagnosis are most likely to arise when liver disease is present or suspected. Such patients have received little attention thus far in this type of study although Schneeberg[19] included some subjects not requiring insulin. Volk and Lazarus[9] did not mention the insulin requirements of their diabetic patients.

MATERIAL AND METHODS

Eleven normal volunteers and 41 patients (38 males and 14 females) were studied by means of an intravenous glucose tolerance test as outlined by Thorn and his associates.[10, 24] Of the 41 patients 34 were studied during a hospital stay, 33 at the New England Deaconess Hospital and 1 at the New England Center Hospital.

All subjects received a diet containing 170-200 gm. of carbohydrate daily for at least two days before the test. In dosage of 0.5 gm. per kilogram of body weight, glucose in a 20 per cent solution was administered intravenously to fasting subjects over a period of thirty minutes, and blood drawn in the fasting state and at thirty, ninety, one hundred and twenty, and one hundred and eighty minutes after the start of the glucose infusion.

The blood sugar was determined by the Folin-Wu method,[25] modified to employ the Somogyi[26] precipitation technic for "true" glucose. Blood samples were allowed to clot for twenty minutes, and the serum then obtained kept at 4°C. Care was taken

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Aided by the Diabetic Fund of Boston.

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to avoid hemolysis. Serum inorganic phosphorus was determined by the Fiske–Subbarow[27] method within forty-eight hours. Serum inorganic potassium was determined on the same samples with the use of the flame photometer.

Except in Cases 47 and 48, all infusions of glucose, collections of specimens and determinations of blood sugar, phosphorus, and potassium were carried out by one of us (K. G.). The over-all errors were 1 or 2 per cent for glucose, 1 or 2 per cent for phosphorus, and 3 or 4 per cent for potassium.

Glucose tolerance was considered to be normal if the following standards were met: a fasting level of 100 mg. per 100 cc. or less (except 107 mg. per 100 cc. in 1 volunteer) and return to the fasting level or below within one hundred and twenty minutes (all but 4 returned to normal in ninety minutes). No significance was attached to the peak blood sugar at thirty minutes (end of the intravenous infusion).

Only 3 patients were taking insulin. Two (Cases 33 and 39) had been receiving 8 units daily, but this was discontinued three days before the test. The other (Case 14) had repeated hypoglycemia until insulin was discontinued, after which all blood sugar values, including those during an oral glucose tolerance test, were normal. Seven additional patients required insulin either before or after the studies.

TABLE 1. *Clinical Data and Results of Liver-Function Tests.*

Case No.	Sex	Age	Clinical Diagnosis before Studies	History						Liver-Function Tests	
				Ketosis	Symptoms	Retinitis	Neuritis	Insulin	Liver Disease	Thymol Turbidity	Thymol Flocculation
		yr.						units		units	
Normal subjects:											
1	M	65	Borderline	0	0	0	0	0	0	0.5	Negative
2	F	49	Borderline	0	0	0	0	0	0	0.8	Negative
3	F	40	No diabetes	0	0	0	0	0	0	2.5	+
4	F	40	No diabetes	0	0	0	0	0	0	2.0	Negative
5	F	27	No diabetes		0			0	0		
6	F	73	No diabetes	0	0	0	0	0	0		
7	F	25	No diabetes		0			0	0		
8	M	60	Diabetes	0	+	0	0	0	0	1.9	Negative
9	M	23	No diabetes		0			0	0		
10	M	54	No diabetes	0	0	0	0	0	0	0.6	Negative
11	M	55	No diabetes	0	0	0	0	0	++++	1.6	0
12	M	44	Borderline	0	0	0	0	0	0	Negative	Negative
13	M	27	Borderline	0	0	0	0	0	0	Negative	Negative
14	M	33	Borderline	0	+	0	0	40	0	Negative	Negative
15	F	32	No diabetes		0			0	0		
16	M	27	No diabetes		0			0	0		
17	M	31	No diabetes		0			0	0		
18	M	35	Borderline	0	0	0	0	0	0	Negative	Negative
19	M	29	No diabetes		0			0	0		
20	M	48	No diabetes		0			0	0		
21	M	42	No diabetes		0			0	0	Negative	Negative
22	M	35	No diabetes		0	0	0	0	0	Negative	Negative
23	F	45	Borderline	0	0	0	0	0	0	1.0	+
24	M	19	No diabetes		0	0	0	0	0		
Diabetic patients:											
25	F	62	Diabetes	+	+	0	0	0	++	2.9	Negative
26	F	60	Borderline	0	±	0	0	0	0	1.4	Negative
27	F	61	Borderline	0	0	0	0	0	0	0.9	Negative
28	M	50	Diabetes	0	+	0	0	0	0	1.4	Negative
29	M	77	Diabetes	0	+	0	0	0	0	1.0	Negative
30	M	54	Borderline	0	±	0	0	(In past)	0	2.5	Negative
31	M	60	Diabetes	0	+	0	±	0	0		
32	M	40	Borderline	0	0	0	0	12*	0	2.2	Negative
33	M	65	Borderline	0	0	0	0	8	0	0.5	Negative
34	M	45	Diabetes	+	+	0	0	50*	++++	12.5	+++
35	M	58	Diabetes	0	0	+	+	0	0	2.5	Negative
36	M	47	Diabetes	0	+	±	0	15‡	0	1.4	Negative
37	M	63	Diabetes	0	+	0	0	0	0	Negative	Negative
38	M	65	Diabetes	±	+	0	+	12*	0	Negative	Negative
39	F	62	Borderline	0	0	0	0	8	0	Negative	Negative
40	M	52	Diabetes	0	+	0	0	0	0	Negative	Negative
41	M	27	Borderline	0	±	0	0	0	0	Negative	Negative
42	F	28	Borderline	0	0	0	0	0	0	Negative	Negative
43	F	57	Borderline	0	0	0	0	0	0	Negative	Negative
44	M	50	Borderline	0	±	0	0	0	0	Negative	Negative
45	M	60	Diabetes	+	+	0	0	120‡	0	Negative	Negative
46	M	72	Diabetes	0	+	0	0	8*	0	0.5	Negative
47	M	56	Borderline	0	0	0	0	0	++++	4.0	
48	M	45	Borderline	0	0	0	0	0	++++	4.6	±
Patients with borderline values:											
49	M	55	Borderline	0	0	0	0	0	0	1.0	Negative
50	M	38	Diabetes	0	+	0	0	0	0	0.7	Negative
51	M	62	Borderline	0	0	0	0	0	0	0.9	Negative
52	M	45	Borderline	0	0	0	0	0	±	Negative	Negative

*Requirements after test.
†Fasting.
‡One year or more before test.

Thirty-five patients had previously been considered diabetic, on the basis of glycosuria and fasting blood sugar values greater than 130 mg. per

toms of diabetes. The 22 patients listed as "Borderline" were so classified because they never had had diabetic symptoms (with the exception of Case 14)

TABLE 1 (*Concluded*).

Case No.	Liver-Function Tests						Liver Size	Highest Blood Sugar	Remarks
	Cephalin Flocculation	Brom-sulfalein Retention	Serum Bilirubin	Serum Albumin	Serum Globulin	Total Cholesterol			
		%	mg./100 cc.	gm./100 cc.	gm./100 cc.	mg./100 cc.		mg./100 cc.	
Normal subjects:									
1	Negative	1.0	Normal	4.0	2.5	277	Normal	198	Pituitary tumor
2	Negative	—	Normal	4.3	2.4	—	Normal	181	Blood sugar 333 mg. per 100 cc. elsewhere
3	Negative	—	Normal	5.6	2.4	—	Normal	126	
4	Negative	—	Normal				Normal	126	Serum protein 5.9 gm. per 100 cc.
5			Normal	6.0	2.2				
6			Normal	4.4	2.3		Normal	95	
7			Normal	5.2	2.8				
8	+	2.4	Normal	4.8	2.5	188	Normal	185	
9			Normal	5.4	3.0				
10	+++	—	Normal			211	Normal	154	
11	++	0	Normal	2.1	4.2	—	Increased	145	Hemochromatosis
12	Negative	—	Normal	5.0	1.9	—	Normal	170	No abnormal blood sugar since 1930; borderline glucose tolerance test.
13	Negative	—	Normal	5.4	2.3	—	Normal	167†	
14	Negative	1.0	Normal	5.4	2.3	181	Increased	155	Normal oral glucose tolerance test
15			Normal	5.2	2.1				
16			Normal	5.2	2.7				
17			Normal	5.4	2.3				
18	Negative	—	Normal	5.0	3.1		Normal	204	
19			Normal	4.8	2.5				
20			Normal	4.8	1.9				
21	Negative		Normal	4.4	3.5				
22	Negative		Normal	4.6	2.7				
23	+	—	Normal	4.6	2.3	—	Normal	179	Strongly positive family history
24	+		Normal	4.0	2.5				
Diabetic patients:									
25	+	19.0	1.4–2	3.2	3.7	231	Increased	333†	Hemochromatosis
26	+	—	Normal	4.4	3.6		Normal	300	
27	++	2.0	Normal	4.7	4.1	198	Normal	200	
28	Negative	Negative	Normal	5.0	2.6	258	Normal	179	Uremia
29	Negative	—	Normal	5.0	2.1	133	Normal	356	
30	Negative	Negative	Normal	4.5	2.4	207	Normal	142†	Positive family history
31			Normal	4.0	3.9	148	Increased	183	
32	Negative		Normal	5.0	3.2	222	Normal	215†	
33	Negative	8.4	Normal	4.5	2.2	146	Normal	187†	Gangrene
34	++++	—	1.9–13.8	3.1	4.2	146	Increased	222†	Hepatitis
35	++	3.0	Normal	4.6	2.9	174	Increased	194	Gangrene
36	+	Negative	Normal	5.6	2.6		Normal	210†	
37	Negative	—	Normal	5.0	2.3		Normal	131†	
38	Negative	2.0	Normal	4.4	2.3	172	Increased	258	Alcoholism
39	Negative	—	Normal	4.8	2.5	282	Normal	171†	
40	Negative	—	Normal	5.0	2.8	241	Normal	177	
41	Negative	—	Normal	5.4	2.1	165	Normal	205	
42	Negative	—	Normal	4.8	1.7	225	Normal	241	
43	Negative	—	Normal	5.4	2.1	261	Increased	218	
44	Negative	7.0	Normal	5.0	2.3	274	Normal	192	
45	Negative	—	Normal	5.4	2.8	181	Normal	940	Coma 1 yr. before
46	Negative	—	0.38–0.9			151	Normal	200	
47		—	6.5–12.5	4.1	2.9	179	Increased	224	Laënnec's cirrhosis
48	++++	—	2.5–3.4	2.4	3.6	111	Increased	182	Laënnec's cirrhosis
Patients with borderline values:									
49	+	6.0	Normal	3.7	2.9	155	Normal	314	
50	Negative	1.0	Normal	4.2	2.5	160	Normal	202	
51	Negative	1.0	Normal			212	Normal	256	
52	Negative	—	Normal	4.8	1.9		Increased	184	Alcoholism

100 cc. (Folin–Wu method) or a blood sugar above 170 mg. per 100 cc. (venous blood) after a meal. Fourteen of this group had experienced symptoms of diabetes; ketosis had occurred in 3, retinitis in 1, neuritis in 2, and peripheral gangrene in 1. In Table 1 these patients are labeled "diabetic" except 1 (Case 14), who had been reported to have elevated blood sugar values elsewhere but who showed normal oral and intravenous glucose tolerance tests here. It is noteworthy that the only person with retinitis had never experienced symptoms and showed no complications attributable to diabetes.

Clinical evidence of liver disease was based on past history or present findings and the repeated observation of gross hepatic enlargement. Some subjects were judged to have possible abnormality of liver function on the basis of minor changes in one or more laboratory tests, or with such changes in addition to hepatomegaly.

Some or all of a battery of liver-function tests were done on each subject.[28] In the normal volun-

teers values for serum proteins and bilirubin (one minute, prompt direct and total) were obtained. In all, bromsulfalein tests were performed in 17, cholesterol levels in 29, serum protein determinations in 38, thymol turbidity, thymol flocculation or cephalin flocculation tests in 39 and bilirubin levels in 40 of the patients with diabetes.

TABLE 2. *Findings during Intravenous Glucose Tolerance Tests.*

Case No.	Sex	Age	Blood Glucose					Serum Phosphorus		
			fasting	at 30 min.	at 90 min.	at 120 min.	at 180 min.	fasting	at 30 min.	at 90 min.
		yr.	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.
Normal subjects:										
1	M	65	75	324	85	68	66		4.7	4.0
2	F	49	94	263	76	79	95	4.5	4.3	4.1
3	F	40	97	387	115	85	70	4.7	3.6	3.1
4	F	40	67	276	79	59	59	4.7	3.9	3.4
5	F	27	89	382	77	83	89	3.5	3.0	3.3
6	F	73	59	352	75	53	76	5.5	4.8	4.6
7	F	25	86	304	68	60	83	4.1	3.4	3.4
8	M	60	95	396	84	54	75	5.5	5.2	4.6
9	M	23	87	383	68	85	90	3.5	3.0	2.6
10	M	54	89	210	109	87	111	4.7	3.5	3.2
11	M	55	88	252	75	69	75	5.1	4.6	5.0
12	M	44	77	396	97	52	47	3.8	3.3	3.3
13	M	27	80	372	83	67	73	4.8	4.2	3.9
14	M	33	82	314	107	72	65	4.0	3.8	3.8
15	F	32	84	256	58	61	76	3.1	3.8	3.5
16	M	27	82	314	57	70	75	2.9	2.3	2.7
17	M	31	79	274	63	83	82	4.7	3.7	3.4
18	M	35	83	316	78	68	68	3.9	3.7	3.9
19	M	29	79	185	61	72	82	4.8	3.6	3.3
20	M	48	76	184	72	72	84	2.9	2.7	3.2
21	M	42	107	364	119	81	74	4.4	3.5	3.2
22	M	35	86	306	60	74	85	4.4	3.2	3.2
23	F	45	86	296	68	57	75	4.0	3.2	3.2
24	M	19	85	348	83	62	81	4.3	3.1	2.8
Diabetic patients:										
25	F	62	120	250	154	135	126	7.5	7.5	6.9
26	F	60	110	378	185	145	104	4.2	4.0	3.5
27	F	61	101	340	170	142	85	3.5	3.0	2.7
28	M	50	80	312	170	139	86	6.7	6.4	5.7
29	M	77	130	400	195	178	138	4.3	3.7	3.3
30	M	54	175	457	314	282	228	4.1	3.7	3.7
31	M	60	112	410	224	158	105	3.9	3.5	3.7
32	M	40	213	421	283	310	265	3.3	2.9	3.3
33	M	65	90	418	192	142	100	5.3	5.1	5.2
34	M	45	138	400	279	240	203	3.7	3.5	3.1
35	M	58	113	376	220	195	140	3.5	3.5	3.3
36	M	47	138	402	217	172	112	4.1	4.0	3.9
37	M	63	113	264	150	124	108	5.1	4.1	4.0
38	M	65	138	414	244	217	177	3.7	3.0	2.7
39	F	62	175	510	356	267	201	4.2	3.9	3.7
40	M	52	147	464	295	253	190	4.0	3.5	3.2
41	M	27	100	390	207	162	97	3.7	3.2	3.2
42	F	28	105	308	167	152	108	4.8	3.8	4.2
43	F	57	107	390	172	127	113	4.2	3.8	3.4
44	M	50	143	470	222	186	129	4.2	3.7	3.1
45	M	60	96	384	183	131	87	4.0	2.8	2.7
46	M	72	135	336	224			4.3	3.6	3.5
47	M	56	104	569	191	195	148	3.2	3.0	2.6
48	M	45	103	274	194	163	115	3.6	3.4	3.0
Patients with borderline values:										
49	M	55	104	406	186	102	76	2.3	2.1	1.8
50	M	38	104	360	158	118	88	4.7	3.5	3.4
51	M	62	124	282	132	114	80	3.5	3.1	3.0
52	M	45	117	358	185	102	75	2.8	2.3	2.2

RESULTS

Table 1 shows the clinical data and results of liver-function tests. Table 2 presents the experimental data in the 52 subjects. Patients are numbered identically in the two tables.

Blood Glucose

Twenty-four subjects showed a normal and 24 others an abnormal glucose tolerance curve as judged by criteria previously outlined (Table 3). Four subjects in the series had curves considered borderline (Fig. 1). The fasting blood sugar ranged between 104 and 125 mg. per 100 cc., and, at ninety minutes all subjects had values over 130 mg. per 100 cc. At one hundred and twenty minutes the blood sugar in all 4 subjects had returned to fasting levels, although it was still above 100 mg. per 100 cc.

Serum Phosphorus

Table 4 shows the average serum phosphorus values in each of the three groups. In the normal subjects the fall varied from 4 to 35 per cent, with an average of 19 per cent. The diabetic patients, however, had an almost identical average fall of 18 per cent, with a minimum of 5 per cent and a maximum of 32 per cent. The 4 "borderline" cases showed an average fall of 22 per cent, with results

varying from 13 to 29 per cent. A considerable overlap in the 3 groups is thus evident.

Serum Potassium

Table 5 presents the changes in the serum potassium in the three groups. In the normal subjects, results varied between a slight rise and a fall of 1.1 milliequiv. per liter; the average fall was 0.33 milliequiv. per liter. The diabetic patients showed a similar variation, with extreme values of +0.25 and −1.0 milliequiv. per liter and an average of −0.32 milliequiv. The decrease in serum potassium in the borderline 4 cases varied between 0.4 and 0.8 milliequiv., with an average of 0.53 milliequiv. per liter. The maximum drop occurred at the end of glucose infusion (thirty-minute specimen) in 22 cases, including 1 borderline, 9 normal, and 12 diabetic subjects. There was no fall or a slight rise in 3 normal and 5 diabetic subjects.

Liver Function

Completely normal liver function and lack of clinical evidence of liver disease were found in 26 cases; the intravenous glucose tolerance test was negative in 17, borderline in 2 and diabetic in 7 of these. The average fall in serum inorganic phosphorus was 19.8 per cent, with a range of 5.0 to 34.6 per cent. Before the test 12 subjects were considered not diabetic, 2 showed borderline oral glucose tolerance tests, and 12 had been considered diabetic.

There were 5 patients (Cases 11, 25, 34, 47 and 48) in whom the diagnosis of liver disease was unquestioned. One of these had negative intravenous and oral glucose tolerance tests. Four were diabetic, both by intravenous glucose tolerance tests and previous clinical study. The average phosphorus

TABLE 2 (*Concluded*).

Case No.	Serum Phosphorus				Serum Potassium					
	At 120 min.	At 180 min.	Fall		Fasting	At 30 min.	At 90 min.	At 120 min.	At 180 min.	Fall
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	%	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*
Normal subjects:										
1	4.0	4.3	0.7	16		3.7	3.7	3.7	4.0	?
2	4.1	4.2	0.4	10	5.0	3.9	5.0	4.9	4.7	1.1
3	3.1	4.3	1.6	34	4.2	4.1	4.6	4.7	4.3	0.1
4	3.4	3.9	1.3	28	5.5	5.3	4.9	5.1	4.8	0.6
5	3.5	3.1	0.5	17	4.7	4.3	4.7	4.6	4.8	0.4
6	4.1	5.5	1.4	24	4.7	4.9	4.9	5.3	5.3	0
7	3.4	3.7	0.7	18	4.5	4.5	4.3	4.1	4.1	0.4
8	4.8	5.0	0.9	13	4.6	3.9	4.5	4.1		0.7
9	3.4	3.0	0.9	31	3.9	4.3	4.2	4.0	3.8	0
10	3.3	4.0	1.5	17	4.4	4.1	4.7	4.6	5.2	0.3
11	5.1	5.1	0.5	10	4.1	4.3	4.0	4.3	4.2	0.1
12	3.2	3.5	0.6	16	4.8	4.4	4.4	4.2	4.6	0.6
13	4.4	5.0	0.9	19	3.8	3.9	3.9	3.8	3.5	0
14	3.7	4.2	0.3	8	4.3	4.2	3.9	3.7	3.6	0.6
15	3.7	3.8	0	10	4.3	4.0	4.1	3.8	3.8	0.5
16	2.8	3.8	0.6	22	3.8	4.0	3.7	3.7	3.5	0.1
17	4.0	4.8	1.3	27	4.4	4.5	3.6	4.6	4.2	0.8
18	4.0	4.1	0.2	4	3.9	3.7	3.9	4.0	4.0	0.2
19	3.3	3.5	1.5	30	4.1	3.8	4.1	4.4	4.0	0.3
20	3.3	3.6	0.2	8	3.6	4.1	4.6	4.3	3.9	0
21	3.2	3.4	1.2	27	4.3	4.0	4.1	4.1	4.0	0.3
22	3.2	3.9	1.2	27	4.2	4.1	3.9	3.9	4.0	0.3
23	3.6	3.4	0.8	20	4.4	4.1	4.3	4.6	4.7	0.3
24	3.2	3.5	1.5	35	3.8	4.3	4.3	4.0	4.1	0
Diabetic patients:										
25	6.9	7.5	0.6	8		3.9	4.8	4.4	4.7	0
26	4.3	4.4	0.7	18	4.2	4.2	4.4	4.5	4.6	0
27	2.5	3.3	1.0	28	5.1	4.3	4.2	4.1	4.2	1.0
28	5.5	5.5	1.2	12	5.5	5.2	4.9	5.1	5.0	0.6
29	3.5	3.3	1.0	23	4.7	4.2	4.6	4.8	4.5	0.5
30	4.0	4.1	0.4	22	4.5	4.6	4.6	4.7	4.6	0
31	3.5	4.0	0.4	10	4.3	3.8	4.0	3.9	3.8	0.5
32	3.3	3.7	0.4	11	4.0	4.5	3.6	3.9	4.4	0.1
33	4.6	5.4	0.7	14	4.7	4.5	4.5	4.7	4.8	0.2
34	3.0	3.3	0.7	31	4.2	4.2	4.2	4.2	4.3	0.1
35	3.2	3.3	0.3	10	5.0	4.3	4.6	4.5	4.5	0.7
36	3.9	4.0	0.2	12	4.3	4.8	4.3	4.5	4.5	0
37	4.4	4.5	1.1	22	5.1	4.1	4.7	4.7	4.7	1.0
38	2.8	2.5	1.2	28	4.2	3.8	4.1	3.6	4.1	0.4
39	3.8	3.6	0.6	12	4.4	4.1	4.2	4.5	4.2	0.3
40	3.0	3.2	1.0	26	3.8	3.6	3.6	3.6	3.9	0.2
41	3.3	3.3	0.5	12	3.4	4.0	4.1	4.2	4.2	0
42		4.7	1.0	21	3.8	3.9	3.9		3.8	0
43	3.7	3.7	0.8	20	4.7	4.4	4.5	4.4	4.4	0.3
44	3.3	3.3	1.1	27	3.9	3.9	4.0	4.0	3.8	0
45	2.9	2.8	1.3	32	4.8	4.2	4.3	4.3	4.3	0.6
46			0.8	19	5.0	4.3	4.8			0.7
47	2.8	2.6	0.6	19	3.1	2.8	2.8	2.9	3.1	0.3
48	2.9	2.8	0.8	22						
Patients with borderline values:										
49	1.9	2.2	0.5	24	4.9	4.1	4.2	4.5	4.8	0.8
50	3.7	4.1	1.3	29	4.8	4.5	4.4	4.4	4.4	0.4
51		3.4	0.5	14	4.3	3.8	4.6	3.6	4.0	0.5
52	2.5	3.0	0.6	20	4.5	4.3	4.1	4.1	4.2	0.4

fall was 15.8 per cent, with a range of 8 to 22 per cent.

The remaining 21 subjects had only suggestive evidence of impaired liver function. The individual findings are indicated in Table 1. In this series, 6 had gross hepatic enlargement with minimal or no abnormality in any liver-function test. Four of these were considered diabetic, 1 borderline, and 1 normal on the basis of the intravenous glucose tolerance test. Before the test, 3 had been considered diabetic, and 3 borderline. The average phosphorus fall was 16.1 per cent, with a range of 9.5 to 27.6 per cent.

Fifteen showed minor abnormalities in one or several liver-function tests. On the basis of the intravenous glucose tolerance test 9 of these were considered diabetic, 1 borderline, and 5 normal. Before the test 3 were considered normal, 9 borderline, and 3 diabetic. The phosphorus fall averaged 19.4 per cent, with a range of 4.4 to 34.0 per cent.

Table 3. *Results of Intravenous Glucose Tolerance Tests.*

Type of Subject	Number	Fasting Value	At 30 Min.*	At 90 Min.	At 120 Min.	At 180 Min.
		mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*
Normal	24	84	311	80	70	74
Borderline	4	112	352	165	109	80
Diabetic	24	124	390	217	176	132

*End of intravenous infusion.

Comparison of Experimental Data with Clinical Findings

Negative Tests

Of the 24 subjects with negative intravenous glucose tolerance tests 16 had never had clinical evidence of decreased carbohydrate tolerance. Eleven were from the volunteer group, and 5 from the patients with diabetes. Of the 8 remaining subjects with normal glucose tolerance 6 had had previously elevated blood sugar values without clinical symptoms; 1 (Case 8) had symptoms of diabetes with glycosuria and hyperglycemia; and 1 (Case 14) had been treated with insulin elsewhere because of symptoms of diabetes and elevated blood sugar values; however, he came to this clinic in marked hypoglycemia, and, subsequently, an oral glucose tolerance test was normal.

Positive Tests

None of the 24 patients with positive intravenous glucose tolerance tests were clinically normal, although in 11 the only abnormality was hyperglycemia; 3 of these (Cases 32, 33 and 39) received small amounts of insulin before or after the test. Twelve had had symptoms or ketosis, or both, as well as elevated blood sugar values. Five (Cases 34, 36, 38, 45 and 46) had previously or have subsequently taken insulin. One patient (Case 30) had experienced questionable symptoms of diabetes with elevated fasting blood sugar values and had taken insulin for five days one year before the test.

Borderline Tests

Three of the 4 patients in this group never had any symptoms of diabetes; in all, however, blood sugar values after eating were elevated. One (Case 50) had previously had symptoms of diabetes.

Except for the 16 described above as clinically normal, all patients had had glycosuria at one time or another.

Discussion

The data presented above suggest that the degree of fall in serum inorganic phosphorus during the intravenous glucose tolerance test has less significance in distinguishing between hyperglycemia due to liver impairment and that due to peripheral underutilization of glucose (diabetes mellitus) than others[10] have postulated. Some of the difference may be due to interpretation. However, although Forsham and Thorn[10] reported a range of 9-39 per cent maximum fall for normal subjects, the ranges in patients with diabetes and in those with liver disease were not given. Furthermore, some of their patients with "liver dysfunction" were said to have entirely negative liver-function tests and yet were stated to have "fatty livers," with no indication of the basis on which the diagnosis was established. In addition they cited a group of 6 patients with normal blood sugar curves characterized by a rapid fall in glucose and a decreased phosphorus fall. They ascribed this to a "depleted liver glycogen reserve" based upon a postulated shorter cycle in the storage of glycogen in the liver with the rapid release of phosphorus. An alternative explanation might be that of Tarail et al.,[20] who found that in some cases the rate of release of phosphate from cells increased despite rapid utilization of glucose, causing a rise in the serum phosphorus levels notwithstanding increased excretion.

It must be emphasized that the diabetic condition of our patients was distinctly "milder" in terms of insulin requirement and blood sugar curves than those studied by Forsham and Thorn.[10] We fully subscribe to the evidence that most patients with

so-called "severe" diabetes show diminished falls in serum inorganic phosphorus as compared to entirely normal persons. It is instructive to note that 1 patient (Case 45), who had entered the hospital a year before in diabetic coma with a blood sugar of 940 mg. per 100 cc., and a carbon dioxide of 4 milliequiv. per liter, required no insulin at the time of our special study, when he showed questionable liver enlargement but negative liver-function tests. The drop in phosphorus was 32 per cent. We believe that he should still be treated as having true diabetes mellitus.

Taub et al.[30] and Forsham and Thorn[10] have indicated that much of the hyperglycemia in elderly patients is largely due to hepatic dysfunction, but we hesitate to take such a stand. Most of our patients belong in such a group, as does a large portion of the diabetic population.[31] The potentially malignant nature of vascular complications in patients whose diabetes seems to be "mild" makes us believe that treatment should be directed toward the diabetes; when liver disease is present, treatment for both conditions should be carried out simultaneously.

Our data show a considerable variation in fall of the serum potassium during the intravenous infusion of glucose in both normal and diabetic subjects, with no significant difference between the two groups in the average maximum decrease. That there was no consistent parallel between the degrees of fall for potassium and phosphorus is in agreement with the findings of Groen and his associates[33] and Roche, deVenanzi and Vera.[32] Such variations in the behavior of serum potassium may be explained in part by the careful studies of Tarail, Seldin and Goodyear,[29] who stated that although in normal subjects the intravenous administration of glucose is accompanied by movement of potassium into cells as glucose is utilized, this is not the only factor in determining the degree of potassium fall. They demonstrated that glucose infusion increases potassium excretion and expands extracellular fluid volume, and suggested that as serum potassium concentration is thus lowered a discharge of potassium from cells occurs. Such a loss, in turn, is counteracted by movement of potassium toward the cells. Further study of potassium during the intravenous glucose tolerance test, along with careful balance determinations, is needed before an accurate interpretation of potassium changes may be made.

TABLE 4. *Composite Values for Serum Phosphorus Obtained during Glucose Tolerance Tests.*

Type of Subject	No. of Cases	Fasting Value	At 30 Min.	At 90 Min.	At 120 Min.	At 180 Min.	Maximum Fall	
							Range	Average
		mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	%	%
Normal	24	4.2*	3.7	3.5	3.8	4.2	35–4	19
Borderline	4	3.3	2.8	2.6	2.7*	3.2	29–13	22
Diabetic	23	4.2	3.7	3.6	3.6*	3.8*	32–5	18

*Data in 1 case not obtained.

TABLE 5. *Composite Values for Serum Potassium Obtained during Glucose Tolerance Tests.*

Type of Subject	No. of Cases	Fasting Value	At 30 Min.	At 90 Min.	At 120 Min.	At 180 Min.	Maximum Change	
							Range	Average
		milliequiv./liter	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*
Normal	22*	4.3	4.2	4.3	4.3	4.2	0 to −1.1	−0.33
Borderline ...	4	4.6	4.2	4.3	4.2	4.4	−0.4 to −0.8	−0.53
Diabetic	23	4.5	4.1	4.2	4.2	4.3	+0.25 to −1.0	−0.32

*Incomplete data in 2 cases.

Summary and Conclusions

Eleven normal volunteers and 41 patients were studied by means of an intravenous glucose tolerance test with concomitant determinations of serum inorganic phosphorus and serum potassium. An evaluation of liver function was made on the basis of history, physical findings and a battery of liver-function tests.

Twenty-four subjects had a normal glucose curve, and the maximum phosphorus fall averaged 19 per cent, with a wide range of 4 to 35 per cent. In the 4 with a borderline sugar tolerance test the maximum decrease in phosphorus was 22 per cent, with a range of 13 to 29 per cent. The 24 diabetic subjects averaged a maximum phosphorus fall of 18 per cent, with a range of 5 to 35 per cent. There was thus no significant difference in the average maximum reduction in phosphorus, and the ranges of values overlapped greatly.

Of the 26 persons with no evidence of impaired liver function 17 showed a normal, 2 borderline and 7 diabetic glucose tolerance; the maximum phosphorus fall averaged 19.8 per cent. Of 5 patients with definite liver disease 4 were diabetic and 1 normal according to the intravenous glucose tolerance test; the maximum drop in phosphorus averaged 15.8 per cent. Among 21 subjects with questionable evidence of liver disease the average phosphorus fall for the 6 with hepatomegaly and for the 15 with minimal abnormality in liver-function tests were 16.1 and 19.4 per cent, respectively.

Decreases in serum potassium averaged 0.33 milliequiv. per liter in the patients with normal glucose tolerance and 0.32 milliequiv. in those with diabetic curves. The ranges of values were almost identical. From these data slight degrees of insulin deficiency could not be distinguished.

The maximum fall of phosphorus during an intravenous glucose tolerance test in patients with lesser degrees of decreased carbohydrate tolerance cannot safely be relied on to differentiate so-called hepatic storage insufficiency from true diabetes mellitus.

Patients with persistent hyperglycemia and glycosuria should be treated as diabetic. If liver disease is present, both conditions should be treated simultaneously.

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GOITER DUE TO LYMPHOCYTIC THYROIDITIS (HASHIMOTO'S STRUMA)*

Its Occurrence in Preadolescent and Adolescent Girls

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IT has long been thought that in preadolescent children most nontoxic goiters not due to carcinoma were of the simple colloid variety. The present report describes observations made on 6 children with goiters that on histologic examination exhibited changes consistent with chronic lymphocytic thyroiditis of the Hashimoto type. The patients were symptom free except for Case 1, who complained of mild dysphagia. None demonstrated any developmental disturbance except Case 3, in which there was considerable retardation in skeletal maturation, a change suggestive of hypothyroidism.

TABLE 1. *Clinical and Laboratory Data in Chronic Lymphocytic Thyroiditis.*

CASE NO.	AGE WHEN FIRST SEEN	HEIGHT	BONE AGE	SIZE OF GOITER	CHARACTERISTICS OF GOITER	SERUM PBI	SERUM BEI	THYROID UPTAKE OF RADIOACTIVE IODINE
	yr.	cm.	yr.			microgm./100 cc.	microgm./100 cc.	%
1	9¼	135		Three times normal	Firm & easily outlined; pyramidal lobe palpable.	8.8	3.7	25
2	9¼	135	9¼	Twice normal	Firm & easily outlined, with nodules; Delphian node palpable.	7.2*	5.6*	35
3	10	132	6	Twice normal	Firm and easily outlined, with nodules; Delphian node palpable.	0.9		44
4	12	150	12	Twice normal	Firm and easily outlined, with nodules; pyramidal lobe palpable.	4.4		25
5	12	147		Four times normal	Firm & easily outlined; Delphian node palpable.	9.6 6.4*	4.2 5.6*	
6	13	161		Four times normal	Firm and easily outlined; pyramidal lobe palpable.	9.3 6.5*	3.9*	84

*During thyroid therapy.

The frequency with which this diagnosis has been made in this clinic may be of interest in view of the supposed rarity of this condition in patients under twenty years of age. Only 11 cases occurring in children could be found in the literature.[1-9]¶

Clinical, laboratory and pathological findings are presented below (Table 1), and the response to treatment is discussed.

OBSERVATIONS

All the patients were girls, a finding that conforms with the sex incidence of this entity in adults.[9, 10] When first seen they were between the ages of nine and thirteen years, the goiters having developed when they were between six and ten years old. There was a family history of thyroid disease in Cases 2 and 6. The former's mother and maternal grandfather had thyrotoxicosis; the latter's maternal grandmother had thyrotoxicosis, and her mother had a goiter of unknown type.

Physical examination showed the thyroid glands of these children to be two to four times larger than normal (Fig. 1) and to be firm, easily outlined and of coarsely granular consistence. Three of the goiters were nodular. In 3 cases the pyramidal lobes were palpable, and in a like number the Delphian lymph nodes|| were enlarged.

The total serum protein-bound iodine concentration (PBI) was abnormally low in Case 3, within normal limits (4 to 8 microgm. per 100 cc.[12]) in Case 4 and abnormally elevated in Cases 1, 5 and 6. In Cases 1 and 5 the butanol-extractable, thyroxin-like iodine (BEI) was also measured. The results obtained by this procedure fell within normal limits of 3.2 to 7.2 microgm. per 100 cc. obtained by Man[14, 15] for adults and of 4.5 to 7.3 microgm. per 100 cc. for infants and children six weeks to ten years old. The forty-eight-hour uptake of radioactive iodine by the thyroid gland varied between a minimum of 25 and a maximum of 84 per cent of the tracer dose (5 to 10 microcuries) given. These

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¶The 3 children mentioned in the series of Statland et al.[10] are included in the present paper. They are Cases 2, 3 and 4. Case 4 was also previously reported.[11]

||Dr. Oliver Cope called attention to a node that in either cancer or thyroiditis may be felt on the trachea just above the thyroid isthmus. Such a node is so indicative of these conditions that he named it the "Delphian node" after the classical oracle.[13]

uptake values bore no clear relation to any of the other clinical or laboratory findings.

Surgical explorations with subtotal thyroidectomies were performed in Cases 2, 3, 4 and 6. On gross inspection, 3 of the specimens thus obtained were found to be of irregular, nodular outline. The fourth was smooth, and all were firm and tan or yellowish white. Microscopical examination revealed extensive lymphocytic infiltration, with germinal-center formation. In most of these glands there was definite hyperplasia of the epithelial cells. Similar microscopical changes were found in the 2 remaining cases, in which biopsies were obtained with the aid of the Silverman needle.[16]

Generous maintenance doses of *USP* thyroid (100 to 120 mg. per square meter of body surface per day[17]) were administered in Cases 1, 5 and 6. In the first 2 of these patients the therapy resulted in considerable shrinkage of the goiter. It also caused the total PBI values to fall and the BEI values to rise to mid-normal levels. In Case 6 there was a fall in total PBI value, but no shrinkage of the goiter; the single BEI value of 3.9 microgm. per 100 cc. obtained while she was receiving 110 mg. of *USP* thyroid per square meter of body surface per day was at a low normal adult level.

Discussion

The 6 patients described here constitute approximately a third of the preadolescent and adolescent children with nontoxic goiters currently under study in the Adolescent Endocrine Clinic of the Massachusetts General Hospital. Those presenting this complaint in the early phases of these observations were subjected to surgical exploration of the thyroid gland to rule out carcinoma. When the clinical characteristics of chronic lymphocytic thyroiditis in children became more fully recognized, needle biopsy was substituted for surgical exploration as the initial step when chronic lymphocytic thyroiditis seemed the most likely diagnosis. Subsequently, as the effects of thyroid therapy on this condition became apparent, the tendency was to omit biopsy if the goiter could be made to disappear

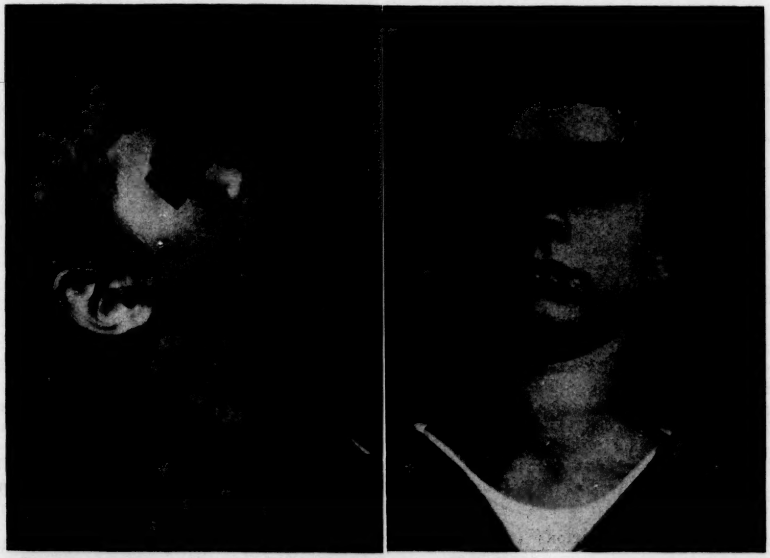

Figure 1. *Goiter Due to Chronic Lymphocytic Thyroiditis. The gland was estimated to be three times larger than normal.*

by administration of generous maintenance doses of thyroid.

The fact that serum PBI values in 3 of 5 cases were abnormally elevated in the absence of symptoms or signs of thyrotoxicosis is considered remarkable in view of the high reliability of this index of thyroid status under most circumstances. This reliability stems from the fact that the total serum PBI is usually made up mostly of thyroxin-like, butanol-extractable, iodinated compounds and only to a minor extent of other, presumably noncalorigenic iodine-containing substances.[14] The finding of low normal BEI values in 2 patients with high PBI values was in keeping with the clinical impression of euthyroidism and indicated that the total serum PBI in these cases was made up to an abnormally large extent of nonbutanol-extractable, calorigenically inactive substances.

These findings could not be explained by a history of ingestion of heavy doses of iodide, parenteral administration of organic iodine compounds or analytic difficulties. There remained the possibility that they were a manifestation of disordered thyroid hormone synthesis and release, as observed in acute radiation thyroiditis and in certain patients with thyroid carcinoma.[18] In other words, it seems a reasonable possibility that in thyroiditis the follicles release either partially proteolyzed or unproteolyzed thyroglobulin or noncalorigenic compounds similar to diiodotyrosine, or both, into the circulation.

When an abnormally large portion of the secretory products of the thyroid gland are physiologically inactive one would expect a tendency to thyroid hormone lack. Thyroid insufficiency normally leads to a compensatory increase in pituitary thyroid-stimulating hormone (TSH) production. TSH in turn leads to enlargement of the gland and to increased secretion of thyroidal substances into the circulation. This homeostatic reaction should continue irrespective either of goiter formation or of the total serum PBI level until the concentration of metabolically active thyroid hormone (BEI) reaches physiologically satisfactory levels. Such a sequence of events could account for the simultaneous occurrence of clinical euthyroidism, goiter, elevated PBI and normal BEI values in Cases 1, 5 and 6. Coupled with a more severe defect in thyroid synthesis, it also could account for the presence of goiter, lowered PBI and retarded skeletal maturation seen in Case 3.

The fact that thyroid therapy could eliminate the goiter and lower total PBI while raising BEI values lends further support to this thesis. It may be assumed that the administered thyroid acted directly to raise the concentration of metabolically active thyroid substances (BEI) in the circulation. This would tend to suppress TSH formation and thereby to reduce thyroid size and secretory activity. In the absence of other sources of nonbutanol-extractable iodine this should result in the normal BEI-PBI relations observed after thyroid administration in Cases 1, 5 and 6.

Conclusions

Chronic lymphocytic thyroiditis is a cause of nontoxic goiter in preadolescent and adolescent girls. It may result in nodules and enlargement of the Delphian lymph node suggestive of thyroid carcinoma.

It may also be characterized by disorders of thyroid hormone release, as demonstrated by abnormal relations between total serum protein-bound and butanol-extractable protein-bound iodine values and a tendency to hypothyroidism. The fact that generous maintenance doses of thyroid can cause this type of goiter to subside suggests that it is compensatory.

We are indebted to the thyroid laboratory under the direction of Dr. Evelyn B. Man, of Yale University School of Medicine, for determination of serum BEI values and at the Massachusetts General Hospital to Dr. Edward Hamlin, Jr., who performed the needle biopsies on two of the patients, to Dr. Benjamin Castleman, who reviewed the pathological aspect of the goiters, and to Dr. John Stanbury, whose group performed the studies of radioactive iodine uptake and most of the serum PBI measurements. We are also indebted to Drs. Douglas S. Riggs and Evelyn B. Man for their helpful advice.

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SPECIAL ARTICLE

GROUP PRACTICE*

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THE term "group practice" cannot be strictly defined. Regardless of description wide variations in size, mode of practice, structure, location and other features are encountered.

One definition[1] is as follows:

> . . . group medicine consists of a group of physicians and dentists who combine their professional services, skills and financial resources to practice the prevention and treatment of disease. These practitioners use common office facilities and professional equipment. They employ in common subsidiary personnel for administrative and clinical purposes.

Another[2] considers group practice a formal association of three or more physicians providing services in more than one medical field or specialty, income from medical practice being pooled and redistributed to the members according to a prearranged plan.

For purposes of eligibility for full membership, the bylaws of the American Association of Medical Clinics contain the following provisions:

> Any group of seven or more full-time physicians maintaining a private organization for the purposes of providing general medical care of high quality . . . shall be eligible for membership. Such group or clinic shall have on its full-time staff at least five physicians in different major specialties, two of which specialties shall be internal medicine and general surgery. Such group shall maintain a separate building or suite of offices for the conduct of its practice.

There are several methods by which group-practice clinics may be classified — by size, by nature of services rendered and by internal structure and organization. Some are large, with physician staffs ranging into the hundreds. Others are small partnerships of three or four men. The majority probably occupy an intermediate position so far as size is concerned. Some provide the immediate community with medical service in much the same manner as individual practitioners, whereas others are principally groups of specialists engaged in referral work and consultations. Most serve both these functions.

Most groups consist of practitioners who have banded together into private organizations. In some, physicians connected with a hospital or medical school have joined in what is surely one kind of group practice. Some groups are sponsored by consumers and are usually known by the name of health co-operatives. In a few cases the establishment of prepaid programs has led to the development of medical groups designed to care for the patients enrolled under such insurance plans. In some groups the physicians are all in one specialty such as radiology, internal medicine or dermatology. All the physicians in some clinics are specialists in various fields; in others physicians in general practice play an important part, and in still others the groups are composed exclusively of general practitioners.

DEVELOPMENT AND GROWTH

Many factors have led to the formation of group practices. Among them are the great increase in specialty practice in the last thirty years and the influence of both world wars. Of 330 listed groups in 1940, 25 per cent were organized within the five-year period of 1919 to 1923, compared with 21 per cent before 1919.[3] When polled during the last year of World War II, over half the physicians in the United States military services indicated that they wished or intended to join groups on their return to civilian life.

Although accurate figures concerning the development of new group practices are not available, it is significant that at least 368 medical groups existed in 1946 and that 91 additional groups came to the attention of the Public Health Service between that year and 1951.[2]

Because it is almost impossible to define and identify all group practices it is difficult to know how many physicians are practicing in groups. One analysis indicates that approximately 2 per cent of all practitioners are full-time physicians on the staffs of groups as shown in 1940 and 1946 studies — 2093 and 3275 physicians respectively. Hunt and Goldstein[2] estimated that there were about 5000 physicians in full-time group practice in 1950 — about 3 per cent of all practicing physicians. Although the statement cannot be accurately documented it is beyond doubt both that the numbers of group-practice units have increased since 1946 and that the proportion of physicians in such forms of practice has grown.

A survey,[4] in 1950 and 1951, of 52 group-practice organizations in California indicated that about 60 per cent were in communities of less than 50,000 population. Many of the groups were small, the average number of physicians in a group being 6 or 7.

Over 70 per cent of the 74 larger groups that were members of the American Association of Medical Clinics in 1953 were located in communities with populations under 125,000.

*Adapted from a chapter entitled "Group Practice" in the forthcoming book *The Physician, His Practice and His Business*, by permission of the publisher, Little, Brown & Company, Boston.

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Hunt[5] lists the following advantages of group practice:

> The principal advantage claimed...is that modern medicine is so complex that no one physician can comprehend all the niceties of diagnosis and treatment, that as a result of this situation, most sick people — if they are to get the best medical care — must be seen by more than one physician and that organization of physicians into groups is the only way in which this can be done efficiently and economically. It is claimed that physicians working together in a group are stimulated to keep up with medical progress more than physicians in individual practice and that each physician, constantly subjected to the informal appraisal of his fellows, has more incentive to do his best work and is less likely to develop slipshod habits of medical practice. The ease and value of consultations is enhanced because the consultant has the patient's whole medical record before him and can more quickly and efficiently bring his own special knowledge to bear on the case.... On the financial side a group of men, by pooling their resources, can maintain equipment for diagnosis and treatment that no one of them could maintain individually and can make efficient use of such expensive items as x-ray equipment. Physicians' incomes are more stable, and some claim that they are larger than incomes in individual practice, at least in the early and late years of practice. The physician in a group is freed from direct financial dealings with patients and is therefore able to do his best work medically without worry about whether he will be paid. He is enabled to take vacations and trips for postgraduate study without jeopardizing his practice or his future prospects. The patient benefits by less expensive service (the usual claim is that he gets more service for the same cost than he would get from an individual practitioner), as well as by the ready availability of competent consultation when he needs it. A well run group is alleged to raise the medical standards of the whole community, by exemplifying modern medical care. Groups have the facilities for, and tend to stress, preventive medicine. By providing nursing and secretarial help economically group organization enables the doctor to spend more of his time doing medical work and relieves him of work that can be done as well or better by less highly trained personnel. A final claim is that group practice facilitates the organization and efficient operation of prepayment plans.

Except in a few states a corporation cannot practice medicine. For this reason the vast majority of group-practice clinics are organized as partnerships. Again, the variation in the details of agreements is remarkable. Some consist of two or three original partner founders, the other physicians in the group serving as employees of the partnership. More often, a definite pattern of entry into the partnership is available for physicians joining the group. A trial period averaging two or three years before admission to the partnership is common, but not invariable. Sometimes a junior partnership has been established as a step preceding the attainment of full partnership status.

Another aspect of most partnerships that should be mentioned is that the more experienced groups have generally found it impracticable to continue indefinitely an equal division of income among the partners or even to weight the influence of all partners in the affairs of the group exactly alike. Consequently, many devices have been adopted to make the partnership structure fit into a smoothly functioning operation. If a corporation could legally practice medicine it would have numerous advantages over the partnership, especially for the groups of larger size. Since it usually cannot, however, a "new" form of group practice has begun to develop. This is an organization that can be described briefly as an unincorporated association of physicians. This structure permits all the physicians in the group to be on a salary established by an elected board of trustees or governors, and therefore it can be operated in much the same manner as a corporation. Furthermore, in this variety of clinic organization, new physicians are generally taken on at the beginning as employees of the association before they are elected to full membership. The association provides considerable flexibility and ease of administration lacking in the partnership and is claimed to facilitate continuity and the coming and going of physician members.

Problems of Organization

The physician contemplating joining a group practice clinic is well advised to have in advance some understanding of the advantages, disadvantages and problems of such association in comparison with those in individual practice. If the various factors are understood, faced and evaluated in advance rather than after two or three years of practice with a clinic much unhappiness and dissatisfaction may be avoided.

The most important problem in the successful operation of a group is the establishment of an equitable and reasonably satisfactory method for the division of the net professional earnings. I believe that there is no "perfect" method of dividing earnings in the sense that every single physician in a group will be satisfied at all times that he is receiving his just deserts. Nevertheless, some methods are certainly much more satisfactory than others.

One method that is employed, at least occasionally, is to divide all net earnings exactly equally among the partners. This has, of course, the advantage of simplicity, but ultimately the earning power, because of specialty and the degree of application of the physicians in a group, will diverge to such an extent that some will justly consider themselves underpaid for their contribution to the group even though the others may not believe that they are overpaid. As a long-term proposition this equal division of net earnings is probably impractical.

Successful group-practice clinics have established a great number of different ways of determining what the income of each partner or physician member of the group should be. Some methods consist of complicated systems in which a certain number of points are assigned to each physician member on the basis of such tangible and intangible factors as bookings, age, length of time with the clinic, attraction of new patients, number of referrals and professional standing. It should be said that these methods have been designed to achieve the equity that is generally desired. Some of them seem to work with reasonable success.

More commonly, perhaps, a larger clinic will have among its members an executive or finance committee that determines the income of each member of the group on the basis of an evaluation of the contribution of each physician. Roughly the same factors often used in the point system are employed under this method. This method has some advantages in flexibility over the point system and permits a physician who thinks he has not been adequately remunerated to meet with the committee determining his income and to present his point of view, and for the committee, in turn, to explain the reasons that determined its decisions. It matters little in practice whether the division of income is managed in this manner under a partnership arrangement or when all physicians are on a salary and salary and bonus are adjusted according to the same criteria. Certainly, the physicians in a group should not expect perfection from any plan to divide their income, but should attempt to make it work as well as possible.

There is one other matter that every physician entering group practice should consider in connection with his expected earnings. If he is a young man entering a properly managed group-practice clinic he can expect what amounts to a ready-made practice with little or no waste of his professional time at the beginning, such as the physician starting in practice by himself often encounters. Nevertheless, the introduction of a new physician into a group lowers the income of the other members, at least during the first year or two of his association, and for this reason he should expect some lag in the subsequent few years between his earning capacity and his take-home income.

Furthermore, it is during the middle professional years of high earning potential that most physicians become dissatisfied — if they ever do — in a group-practice clinic. This is because they see colleagues and classmates in individual practice in the same field who may be earning a great deal more. In all probability, however, given two equally competent and successful physicians, one in group practice and the other practicing alone, the lifetime earnings after overhead and taxes are deducted differ very little; the income of the group-practice physician is likely to be higher at the beginning, lower in the middle years and reduced less rapidly in the later years of his professional career. At any rate, these matters should be frankly considered in advance, and the choice taken with one's eyes open.

Enough has been said already to indicate that entry into group practice presents many continuing problems as well as advantages. Perhaps because of the innumerable difficulties in establishing a group-practice clinic many of those now in existence have been and some are still operated as one-man autocracies. The autocratic head of a group must battle through many of the problems mentioned — and others — and often can do so more efficiently and effectively than a more amorphous group structure. The fact that there is only one head of the group and that all unresolved matters are referred to and decided by him frequently leads to smooth functioning even though there is much grumbling. There is little doubt that many group-practice clinics would not be in operation today if it had not been for the forceful and successful efforts of autocratic founders.

In the nature of things an autocratic structure, if it was the original form, cannot continue indefinitely. When the time comes for it to change, a crisis often faces the clinic. The pressures for increased representation by the professional staff are generally irresistible, but if leadership is lacking, a state of utter confusion may arise. Without going into the technical problems involved, I can only say that this phase of evolution involves a compromise between the desirable features of democratic representation and the necessary development of leadership and administrative abilities. That this has been accomplished successfully in many places attests to the feasibility of such an evolutionary process.

With increasing frequency group-practice clinics are establishing fringe benefits of considerable value to the physician: time off and financing for medical meetings or graduate courses, specified time for sick leave and vacations, group life insurance and, most recently, efforts to develop satisfactory pension plans. The nature of these benefits vary, of course, from one group to another, but are factors to be taken into consideration by the members of the professional staff as well as the nonprofessional employees.

Some groups rent office space more or less indefinitely and thus have a problem differing little from that of the individual physician, who must also pay rent. The majority of the private clinics, however, have considerable investment in buildings and equipment, usually built up by capital paid in by the physicians in the group. In some cases the investments are extremely large, posing a problem when an original partner or member retires, dies or leaves the group, or when a new physician joins it. In a similar way the setting up of reserves for expansion and the purchase of new equipment frequently presents a problem.

Many devices have been adopted to facilitate the orderly transfer of capital from older to younger physicians. Some are more successful than others. At present, in private medical clinics, there is an increasing tendency to manage this problem through the medium of a corporation or nonprofit foundation separate from the partnership. As time goes on the problem is apparently being solved with greater and greater success. The necessity for so doing is the greater because of the difficulty with which even successful younger physicians are faced in

saving enough from their incomes to invest in capital expenses in the present days of high income taxes.

None of the problems enumerated, or the others with which group-practice clinics are commonly faced, seem to be insoluble. It is likely, however, that both the group as an entity and the professional individuals in it must have a desire to meet the problems as they arise and to make things work or insurmountable difficulties may develop.

Possibilities for the Future

The development of group practice is a strictly North American contribution to the mechanics of rendering medical care, and a partial answer to the growth of specialism during the past half-century. It gives every evidence of being here to stay, though its patterns of development are still in process of evolution, and eventually several different forms will presumably emerge as being best adapted to differing circumstances.

It is significant that this development has resulted in the establishment of two national organizations in the field of group practice: the National Association of Clinic Managers and the American Association of Medical Clinics. The business aspects of a successful group are obviously considerably more complicated than those of individually practicing physicians. The first organization in the field, therefore, was the National Association of Clinic Managers, organized in 1926 and testifying to the fact that all other aspects of group practice would fail unless enough money was available to pay the medical and nonmedical personnel, and to purchase equipment and services. This association has held annual meetings and has collected a vast amount of information on the business aspects of group practice. It has rendered the medical profession great service in gathering information concerning appropriate business methods and in standardizing certain types of business procedures. There is no foreseeable end to the contribution that this organization can make to the field of business management as related to group practice.

The American Association of Medical Clinics, an organization of group-practice clinics in the United States and Canada at the professional level, was established in 1949. Its purposes are to elevate the standards of practice, foster and improve graduate medical education and promote medical research in medical clinics, to give mutual help by the interchange of ideas and experiences of member clinics and to disseminate scientific and medical knowledge, particularly as it pertains to the practice in medical clinics. Some of its activities are consequently significant for physicians considering entry into group practice.

The Association holds an annual meeting at which many problems peculiar to this type of practice are discussed, including internal structure and problems of groups, their relation to prepaid medical care plans and similar matters of special interest. The proceedings of these meetings and other information are published in the Association's *Bulletin*, currently issued six times a year.

The Association issues a directory of its members, giving the professional staff members and their fields of specialty. It is actively pursuing a study of the role of group-practice clinics in the provision of graduate medical education in conjunction with the Council on Medical Education and Hospitals of the American Medical Association and the Advisory Board of Medical Specialties. Likewise, it is engaged, with the Council on Medical Service of the American Medical Association, in a survey of group practice aimed at developing information that would be of value to physicians desiring to start a group practice or to group-practice clinics that have problems with which they need assistance.

Finally, of interest to some, is the placement service offered by the Association to physicians desiring to associate themselves with a group practice and to group-practice clinics that desire additional professional personnel. These constitute only a few of the activities in which the Association has become involved in its brief existence.

Conclusions

Group practice offers attractions to the practicing physician in many respects, probably aids in providing improved medical care to many communities, but poses many problems of operation. The number of group-practice units and the number of physicians associated with this form of practice are both gradually increasing.

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MEDICAL PROGRESS

THE CARDIAC ARRHYTHMIAS (Concluded)*

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LOS ANGELES

ARRHYTHMIAS ARISING IN ATRIOVENTRICULAR NODE

There is both experimental and clinical evidence[11] that extrasystoles and tachycardia originating in the atrioventricular node often cannot be differentiated from corresponding arrhythmias arising elsewhere in the atria. Ectopic rhythms initiating from foci in the midportion of the atrium failed to yield P′ waves in standard leads. Since only QRS complexes were visible the electrocardiogram was indistinguishable from that of nodal tachycardia. In contrast upright P′ waves were recorded when the focus was at the cephalic end of the atrium. Inverted P′ waves occurred when the focus was at the caudal end. Some atrial arrhythmias with long PR intervals presented an electrocardiographic pattern similar to nodal tachycardia because the P′ waves appeared to follow the QRS complexes. Daines and Hecht[75] reported the production of nodal rhythms in human subjects by intravenous injection of 1 mg. of Neo-Synephrine Hydrochloride.

Several investigators[76-78] have concluded that supraventricular arrhythmias associated with the Wolff–Parkinson–White syndrome arise in or near the atrioventricular node. Experimental evidence was presented that a disturbance in part of the node may produce all phenomena of the syndrome.[55] Accelerated conduction occurred through the disordered portion of the node, causing typical Wolff–Parkinson–White patterns in the electrocardiogram. The nodal defect sometimes functioned as an ectopic focus, giving rise to various supraventricular arrhythmias. Whether nodal rhythm, extrasystoles, tachycardia, flutter or fibrillation developed depended on the rate of discharge of the nodal focus. These observations conflict with the common belief that the Wolff–Parkinson–White syndrome represents transmission of impulses over an aberrant anatomic atrioventricular bundle.

Several clinical cases consistent with the preceding experimental findings were described by Lown et al.[79] The patients presented short PR intervals, normal QRS complexes and episodes of supraventricular tachycardia. In the opinion of the authors the findings could not be attributed to conduction over an aberrant atrioventricular connection.

VENTRICULAR ARRHYTHMIAS

Mechanism

Probably because the ventricular arrhythmias are relatively uncommon, their mechanism has been subjected to much less study than that of the atrial arrhythmias. Disturbances of the ventricular rhythm are nevertheless of sufficient clinical importance to warrant a continuation and intensification of recent investigations.

Scherf et al.[80] produced ventricular tachycardia by applying aconitine to a localized area of the ventricular myocardium. When the aconitine focus was cooled, sinus rhythm recurred. These observations were confirmed and extended by other workers using electric as well as chemical methods of production.[81] The contraction waves of ventricular extrasystoles and tachycardia could be clearly seen in high-speed cinematographs of the relatively thin-walled right ventricle. During both arrhythmias contractions appeared to spread out radially in all directions from the focus.

Harris and his associates[82] recorded electrocardiograms of the ventricular tachycardia associated with experimental myocardial infarction. Isoelectric intervals separated the QRS complexes in many of the tracings, indicating that intraventricular conduction was not continuous. The conclusion was drawn that the arrhythmia probably resulted from a discharging ventricular focus rather than from a re-entry phenomenon. A similar conclusion concerning the mechanism of ventricular tachycardia produced by electric stimulation was suggested by the experiments of Osborne and his co-workers,[83] who observed that very narrow QRS complexes and long isoelectric intervals appeared when the focus of the tachycardia was near the apex of the septum. Such patterns were considered inconsistent with the presence of continuous ventricular activity, which presumably would occur during circus movement.

Transitions between the ventricular arrhythmias were observed experimentally as the rate of discharge from an ectopic focus gradually increased.[81] The arrhythmias could be produced seriatim by mechanical, chemical or electric stimulation of the ventricle. Electrocardiograms recorded during the experiments showed extrasystoles of increasing frequency, followed by typical tachycardia complexes occurring at progressively higher rates. The isoelectric interval shortened as the rate increased, finally disappearing to produce a "flutter" pattern. A further increase in the atrial rate usually precipi-

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tated fibrillation. In contrast to atrial fibrillation produced by application of aconitine the ventricular fibrillation initiated with this chemical could not be abolished by cooling of the focus.

In comparison between high-speed cinematographs of experimental atrial and ventricular fibrillation,[81] cinematographs of the ventricle proved more difficult to interpret than films of the atrium. Because the ventricular wall is relatively thick finer details of its contraction were often obscure to the observers. Within the limits of the technic the fibrillating ventricle was seen to display constant activity comparable to that found in the fibrillating atrium. Many large waves appeared to travel variable distances in a more or less co-ordinated manner but were suddenly replaced by newly formed waves traveling in the opposite direction. Superimposed on the large waves were innumerable asynchronous waves apparently involving small groups of individual muscle fibers. Nothing suggesting a circus movement could be found.

Etiology

The occurrence of ventricular arrhythmias during surgical operations has aroused much interest in recent years.[84] These disturbances may arise not only when the heart is within the operative field but also during thoracic and general surgery. Extrasystoles resulting from manipulation of the heart or its neighboring structures are commonly observed. The more serious arrhythmias, however, cannot be closely correlated with the type of operative procedure. Apparently, more important etiologic factors are the kind and depth of anesthesia, the degree of hypoxia and reflexes arising from stimulation of the vagus.[84, 85] These observations emphasize the value of control of anoxia and of large and repeated doses of atropine to minimize vagus effects on the heart.

Ventricular arrhythmias as a potentially serious complication of human cardiac catheterization have been discussed.[42a, 43, 86, 87] Goldman et al.[88] found premature ventricular systoles in 88 per cent, short runs of ventricular tachycardia in 78 per cent, ventricular flutter in 6 per cent and ventricular fibrillation in 2 per cent of cases in which cardiac catheterization was performed. Southworth and his associates[89] described a case of nonfatal ventricular fibrillation occurring during this procedure. Bruce and his co-workers[86] noted a prolonged and serious paroxysm of ventricular tachycardia precipitated by catheterization in a patient with the Wolff–Parkinson–White syndrome. A case of fatal ventricular fibrillation precipitated by catheterization in a child with the syndrome was reported.[89] The increased susceptibility to serious or fatal arrhythmias in such cases may be considered as a relative contraindication to cardiac catheterization.

The recent literature includes a case of ventricular tachycardia resulting from carotid-sinus stimulation[90] and one of ventricular fibrillation precipitated by pressure on the eyeball.[91] A number of drugs have been implicated as etiologic factors in ventricular arrhythmias. Among these are Etamon (tetraethylammonium chloride),[92] as well as the combination of caffeine, amphetamine and Coramine (nikethamide) used for treating barbiturate poisoning[93] and Dilantin (diphenylhydantoin sodium) intoxication.[94] As discussed later, digitalis, quinidine and Pronestyl (procaine amide hydrochloride) are also capable of inducing serious disturbances of ventricular rhythm. An unusual case of digitalis toxicity was reported[95] in which ventricular tachycardia with collapse followed a single oral dose of 0.6 mg. of digitoxin.

Potassium intoxication such as may occur in the presence of renal insufficiency[96] frequently gives rise to ventricular arrhythmias. Extrasystoles, tachycardia, fibrillation and ventricular standstill may result from elevation of serum potassium levels.

Emotional disturbances are capable of precipitating ventricular as well as atrial arrhythmias in both normal and diseased hearts. Emotional stress as an etiologic factor in ventricular extrasystoles has been discussed in several reports.[44-46] Harvey and Levine[97] reported a case of paroxysmal ventricular tachycardia induced by apprehension in a patient with a normal heart. They suggested that this case may throw light on the mechanism of "death from fright."

Mann and Burchell[98] presented evidence that ventricular extrasystoles that occur only during exercise are highly suggestive of coronary insufficiency. These authors emphasized the importance of treating such extrasystoles to prevent the onset of a more serious arrhythmia and also to increase tolerance to exercise.

Clinical Aspects

The difficulty of differentiating some cases of ventricular tachycardia from supraventricular arrhythmias, particularly from atrial fibrillation with aberrant ventricular complexes, has been discussed by several authors.[99-102] Osborne et al.[83] noted that the complexes of ventricular tachycardia may be of normal width, the electrocardiogram resembling that of a supraventricular arrhythmia. The narrow QRS complexes occurred when the ectopic focus was near the apex of the septum so that both ventricles contracted simultaneously in a relatively normal manner. Cinematographic studies have shown that such contractions can effectively expel the contents of the ventricles. When the ectopic focus is near the base of the heart the contraction wave spreads toward the apex; this type of wave cannot expel blood efficiently. Atrial tachycardia occurring at comparable rates is not as serious as ventricular tachycardia since cardiac efficiency is much less affected.

Dressler and Roesler[103] suggested that the diagnosis of paroxysmal ventricular tachycardia at rates below 150 per minute may be facilitated by the finding of occasional ventricular complexes resembling beats of sinoatrial origin. The importance of ventricular tachycardia and fibrillation as a cause of Stokes–Adams attacks, both in patients with complete heart block and in those with normal atrioventricular conduction, is now recognized.[104-107]

Schwartz et al.[108] noted that the establishment of ventricular fibrillation in patients with atrioventricular dissociation was usually preceded by a prefibrillary period sometimes lasting many minutes. The manifestations of this period began with a lability of ventricular rate followed by the appearance of ventricular premature beats. Recurrent short bursts and runs of deformed, bizarre complexes then occurred. The final stage consisted of more or less prolonged ventricular fibrillation. Prompt recognition of these prefibrillary signs may permit the institution of prophylactic treatment to prevent actual fibrillation.

Froment, Gallavardin and Cahen[109] emphasized the well known fact that ventricular tachycardia presents an extremely variable clinical picture. The following clinical classification was proposed: terminal prefibrillatory tachycardia, occurring in the presence of serious underlying heart disease and always fatal; ventricular extrasystoles with paroxysms of ventricular tachycardia, a less serious form of ventricular tachycardia occurring in otherwise healthy hearts; ventricular paroxysmal tachycardia due to septal lesions, usually infarction or syphilis; and major paroxysms of ventricular tachycardia in young subjects with normal hearts. These arrhythmias were considered to be the clinical counterpart of paroxysmal atrial tachycardia.

Armbrust and Levine[110] presented an extensive review of 107 cases of paroxysmal ventricular tachycardia. Seventy-four per cent of the arrhythmias occurred in patients with coronary-artery disease, 8.4 per cent in patients with rheumatic heart disease, and 12 per cent in normal hearts. The authors re-emphasized the fact that ventricular tachycardia should be suspected at the bedside in the presence of changing intensity of the first heart sound, slight but detectable irregularities of the cycle length, failure of vagal stimulation to produce any effect and a jugular pulse rate slower than the ventricular rate. In a few of the cases analyzed, only one heart sound was audible with each beat. This unusual finding led to an initial erroneous determination of the rate at half its actual value. In 5 cases an arrhythmia presenting the electrocardiographic pattern of ventricular tachycardia occurred as a serious or fatal complication of the Wolff–Parkinson–White syndrome, which may thus result in sudden death.

Recovery from ventricular fibrillation associated with acute myocardial infarction has been reported by Daniel and Magruder.[111] Another unusual case report concerns paroxysmal ventricular tachycardia occurring after myocardial infarction and persisting for fifty-seven days.[112]

Treatment

As a result of continuing research the morbidity and mortality associated with cardiac arrhythmias have been markedly reduced. The chief advance in pharmacologic treatment during recent years was the introduction of procaine amide, known as Pronestyl. This preparation now occupies a place among the mainstays of antiarrhythmic therapy — namely, the digitalis glycosides, quinidine and carotid-sinus stimulation. Paralleling in importance the advent of Pronestyl are the advances in treatment of cardiac arrest.

Pharmacology of Antiarrhythmic Drugs

Recent observations on the mechanism of arrhythmias have stimulated renewed interest in the pharmacologic action of antiarrhythmic drugs. According to proponents of the circus-movement theory the antiarrhythmic property consists of an effect on the refractory period and on conduction velocity of heart muscle. By lengthening the refractory period or increasing conduction velocity, or both, the drug is believed to close the "excitable gap" on the circus pathway. An impulse traversing the pathway is presumably blocked when it reaches refractory muscle that it cannot re-enter. Thus, the self-perpetuating circus movement is interrupted, and the arrhythmia terminates.

Several observations that appear to conflict with this hypothesis were recently reported. Wedd, Blair and Warner[113] noted that the antiarrhythmic property of a drug is not completely dependent on its ability to prolong the refractory period. Gilbert and his co-workers[114] described cases in which quinidine abolished fibrillation with little prolongation of refractoriness. Woske et al.[115] found that the antiarrhythmic action of procaine amide resides principally in the ability of the drug to depress the excitability of cardiac muscle. These workers reported that procaine amide exerts an antifibrillatory effect without necessarily prolonging the refractory period in the ventricles. They further observed that procaine amide decreased conduction velocity. Theoretically, an agent must increase conduction velocity or lengthen the refractory period to terminate arrhythmias involving circus movement.

An alternative explanation of the action of antiarrhythmic drugs has been proposed by workers who believe that arrhythmias result from repetitively firing ectopic foci. Evidence was presented that quinidine delays recovery of both atrial excitability and atrial conductivity after the absolute refractory period.[11] It was pointed out that either of these two effects tends to slow the rate of discharge from an ectopic focus. Depression of excitability rather than depression of conductivity was

held responsible for the antiarrhythmic action of quinidine. Since fibrillation was regarded as a form of advanced conduction failure, drugs that delay conduction recovery were considered profibrillatory. Quinidine, however, was found to depress excitability more drastically than it depressed conduction recovery, thereby accounting for its net antifibrillatory effect.

A different conclusion concerning the action of antiarrhythmic drugs was drawn by Farah and Loomis,[116] who studied the action of cardiac glycosides on atrial flutter produced by the crush method of Rosenblueth and Garcia Ramos.[13-15] The arrhythmia was assumed to involve a circus movement. When glycosides were given after denervation of the heart a decrease in atrial rate or reversion to normal sinus rhythm occurred. In the innervated heart, lanatoside C caused flutter to change to fibrillation. These results were believed to indicate that the direct action of the drugs is to increase refractoriness and decrease conduction velocity, whereas the reflex vagal action decreases the refractory period and increases conduction velocity.

Brown and Acheson[117] made the interesting experimental observation that arrhythmias produced by different methods may respond differently to an antiarrhythmic drug. Atrial flutter produced by aconitine showed an initial slowing of the atrial rate after administration of quinidine, culminating in restoration of normal sinus rhythm. In flutter caused by the "crush" method quinidine abolished the arrhythmia abruptly, without preliminary slowing of the rate. As seen clinically, the atrial rate decreases before reversion to regular sinus rhythm when quinidine is given to patients with spontaneous flutter. These observations may thus be considered evidence that clinical flutter is analogous to the chemically produced arrhythmia resulting from a rapidly discharging ectopic focus.

Purified digitalis preparations. Oral preparations such as digitalis leaf, digitoxin, gitalin and Digoxin are commonly used in the treatment of cardiac insufficiency. In contrast, except for the purpose of influencing atrioventricular block as in atrial fibrillation, the oral digitalis preparations have proved of limited value in patients with arrhythmias. Lanatoside C is the form of digitalis most widely used for antiarrhythmic therapy. This drug acts rapidly and is eliminated quickly. Moe and Mendez[118] attempted to determine if any cardinal differences other than speed of action and elimination existed between the various cardiac glycosides. Digitoxin, ouabain, lanatoside C, and K strophanthoside were studied. These preparations showed no major qualitative difference in their influence on excitability, on atrioventricular and intraventricular conduction or on the ability of myocardium to develop ectopic foci.

The therapeutic use of lanatoside C in supraventricular tachycardias has been reviewed by Levenson and Thayer[119] and others.[120-122] Barrow[123] reported that 26 cases of paroxysmal supraventricular tachycardia were converted to normal sinus rhythm with intravenous injection of lanatoside C. No serious toxic symptoms occurred in this series. The patients presented a variety of diseases including pneumonia, cholecystitis, pulmonary embolism, acute alcoholism, rheumatic valvular disease and cirrhosis. Dosage of lanatoside C ranged from 0.8 to 2.0 mg., averaging 1.2 mg. Gilson and Schemm[124] described several cases of uncomplicated ventricular tachycardia that, contrary to general belief, showed no harmful effects from administration of digitalis. Shapiro, Weiner and Bernstein[125] also reported benefit from digitalis in "benign" ventricular tachycardia not complicating myocardial infarction. Most cases of ventricular tachycardia, however, occur in association with myocardial infarction. Under such circumstances, administration of digitalis may be dangerous. The differential diagnosis between ventricular tachycardia and extreme atrial tachycardia or fibrillation with aberration is often difficult.[101, 102]

Successful use of lanatoside C in the treatment of supraventricular tachycardia in an infant with the Wolff–Parkinson–White syndrome was reported by Gleckler and Lay.[126] Fenichel[127] employed digitalis for the unusual purpose of producing atrioventricular block in a patient with uncontrollable paroxysmal atrial tachycardia. Digitalis was also used successfully in a patient exhibiting intractable episodes of atrial flutter with rapid ventricular rate.[128] The paroxysms of flutter continued after digitalization, but the ventricular rate was slowed.

Ouabain is a digitalis preparation of great value in emergencies. This drug has been in general use abroad for many years and is now becoming more widely employed in America. Since ouabain acts even more rapidly than lanatoside C it may be given when an immediate effect is urgently required.[129] A dose of 0.5 mg. followed every hour by 0.1 mg. should be administered.[120] According to Kisch[130] the drug should be diluted in 500 cc. of glucose and given slowly as a drip infusion over a period of not less than three hours. In emergencies, however, a much smaller volume of diluent and much more rapid administration are necessary.

Acetyl strophanthidin, a synthetic ester of the cardiac aglycone strophanthidin, was studied by Enselberg et al.[131] Restoration of normal rhythm was achieved with this drug in 11 of 12 cases of supraventricular tachycardia. Acetyl strophanthidin is the most rapidly acting digitalis-like preparation available. Its effects appear in one to five minutes, and the peak of action occurs within sixteen minutes of administration. Burrell and Goggins[132] reported the development of fatal ventricular fibrillation after administration of acetyl strophanthidin. Acute intoxication, sometimes with ominous toxic rhythms, has also been observed.[133] In view of these reactions

the use of acetyl strophanthidin as an antiarrhythmic measure may be inadvisable. We have found that ouabain acts with sufficient rapidity and is considerably safer.

Quinidine. Despite exaggerated fears concerning its dangers, and despite the advent of Pronestyl, quinidine has retained its importance as an antiarrhythmic agent. Sokolow's[134] comprehensive review emphasized its salient properties and therapeutic value. Goldman,[135, 136] reviewing his experience in the treatment of atrial fibrillation, concluded that judicious use of this valuable agent yields excellent results. Quinidine converted the arrhythmia to sinus rhythm in 87 per cent of the cases described by Yount, Rosenblum and McMillan,[137] and was found by them and by Goldman to be highly effective in chronic fibrillation. Comparable results with Pronestyl have not been demonstrated.

Of the available preparations for parenteral administration quinidine lactate and gluconate have both proved effective. Harris et al.[82] reported that the combination of quinidine gluconate and morphine sulfate yielded a more consistent antiarrhythmic effect than either quinidine gluconate alone or quinidine lactate alone or with morphine. Sampson, Foreman and Solomon[138] contributed a useful clinical observation by demonstrating the value of enteric-coated, slowly absorbed quinidine tablets; when the tablets were taken at bedtime the patient did not need to be awakened for medication during the night. Recent clinical cases illustrating the antiarrhythmic properties of quinidine were reported by Greenfield and Reiss,[139] January, Hamilton and Sinton,[140] Bell, Bradley and Hurxthal[141] and Chapman.[142] In 1 case, a ventricular tachycardia that persisted despite oral administration of Pronestyl was only temporarily controlled by intravenous injection of Pronestyl but responded well to small doses of quinidine sulfate by mouth.[142] Schack, Hoffman and Vesell[143] also noted cases in which quinidine proved effective after Pronestyl therapy had failed. Moss and Thompson[144] found quinidine effective in an infant with paroxysmal tachycardia that had failed to respond to digitoxin.

The opinion is frequently expressed that quinidine should be administered intravenously only in grave emergencies. Recent experience suggests that this rule may not apply when the drug is given according to the technic proposed by Clagett.[145] The quinidine lactate is diluted in 50 to 150 cc. of 5 per cent glucose and introduced into the vein by the drip method at a rate of 2 cc. per minute. Electrocardiograms should be taken frequently throughout the injection, so that the drug may be discontinued at the first sign of toxicity. This method may involve less danger than intramuscular administration because the intravenous drip can be discontinued immediately on restoration of normal rhythm. In contrast, when the intramuscular route is used, absorption of the drug may continue for some time after the desired effect has been obtained, and the risk of toxic manifestations after termination of the arrhythmia is thus increased.

As a result of refinement in technic the determination of blood quinidine levels has become a useful laboratory procedure.[146-148] Although the value of these studies has been subject to question[149] two important clinical benefits may be noted. In the first place more effective dosage schedules of quinidine can be determined. Secondly, the patient need not be exposed to possible toxic effects that result when dosage is increased after a high blood concentration (9 to 10 mg. per liter) has already been reached.

Sokolow and Edgar[148] and Kalmansohn and Sampson[146, 147] showed that the antiarrhythmic property of quinidine depends on maintenance of a critical threshold blood level. The threshold level varied in different cases but was constant in a given patient. This observation has been applied to the two theories concerning the mechanism of atrial flutter and fibrillation. Lewis et al.[150] postulated that failure of quinidine to terminate circus movements was attributable to a conduction-depressing action of the drug that counterbalanced its effect of lengthening the refractory period. If this explanation is valid an increase in the blood level of quinidine would cause further depression of conductivity as well as further lengthening of the refractory period. Regardless of the blood level, therefore, quinidine could not exert an antiarrhythmic action unless it affected the refractory period more drastically than it affected conductivity. No such differential action need be postulated to explain the threshold blood level of quinidine if atrial flutter and fibrillation result from a rapidly discharging ectopic focus. According to this theory the arrhythmia would terminate when quinidine was present in sufficient concentration to depress effectively the excitability of the focus. The threshold blood level of quinidine would thus depend on the resistance of the focus to the drug. Relatively low concentrations presumably would eliminate a weak focus, and larger concentrations would be required to eliminate a well entrenched focus.

Among the toxic effects of quinidine recently noted were febrile hypersensitivity[151-153] and allergy manifested by chills, fever, thrombocytopenia and a maculopapular eruption.[154] Paroxysmal ventricular tachycardia and fibrillation were also attributed to quinidine.[155] Brown et al.[156] demonstrated in patients with congestive heart failure that quinidine disappeared relatively slowly from the blood stream. Such patients were therefore more likely to display signs of quinidine toxicity, especially ventricular tachycardia. Several cases of thrombocytopenia purpura after treatment with quinidine were reported.[157-160] One group[159] concluded that the disturbance was an antigen-antibody type of reaction resulting in increased destruction or removal of

platelets. Others[160] believed that inhibition of platelet formation by the megakaryocytes also occurred.

Procaine amide (Pronestyl). As discussed by Schaffer,[161] undesirable side effects formerly limited the use of procaine in concentrations adequate to control arrhythmias. With the introduction of Pronestyl by Mark et al.,[162] these reactions were largely abolished, and the drug now enjoys wide usage.[163-169] Except for minor toxic effects, Pronestyl is relatively harmless in most cases. Rarely, the drug gives rise to serious reactions such as ventricular arrhythmias,[170-173] atrial arrhythmias,[174] agranulocytosis,[175, 176] dermatoses[177] and psychosis.[165]

Pronestyl was originally believed to be of therapeutic value only in ventricular arrhythmias,[162] but recent experience has established its usefulness in the management of atrial arrhythmias as well.[178, 179] The drug may be given orally,[165] intramuscularly[167, 169] or intravenously.[180] The usual oral dose is 250 to 500 mg. repeated in two hours. Much larger amounts are sometimes necessary to abolish a rapid arrhythmia. Large doses frequently induce minor reactions such as nervousness, nausea and vomiting, choking sensations and diaphoresis.[168]

Since Pronestyl is rapidly effective when given intramuscularly, the intravenous route is rarely required except in profound shock when absorption from muscle is poor. The rate of intravenous injection should not exceed 100 mg. per minute.[180] Large doses given by vein may have a considerable hypotensive effect. Nor-epinephrine has been found useful in restoring normal blood pressure.[181]

Pronestyl has been considered preferable to quinidine when intravenous medication is indicated.[182] As noted above, this conclusion may not be warranted if quinidine is given by the method of Clagett.[145] Evidence has been presented that both Pronestyl and quinidine are highly effective in abolishing atrial fibrillation of recent origin.[179] Quinidine appears more effective than Pronestyl in converting chronic atrial fibrillation to sinus rhythm. When Pronestyl was first introduced it was considered far superior to quinidine in the treatment of ventricular arrhythmias. More recent studies indicate that this difference in efficacy is probably less than was originally supposed.

An impression seems to have arisen that Pronestyl should replace quinidine. In our opinion this point of view is not substantiated by available evidence. Although cases have been reported in which Pronestyl succeeded after quinidine failed,[183-185] it cannot be concluded that Pronestyl is necessarily superior unless both drugs are given by the same route and in comparable doses.[185] Clinical series of cases large enough to provide statistically significant data must be studied before valid conclusions can be drawn concerning the relative merits of Pronestyl and quinidine.

Carotid-Sinus Stimulation

This simple form of therapy continues to occupy a respected position in the antiarrhythmic armamentarium because of its frequent effectiveness in abolishing paroxysms of atrial tachycardia. The proper technic has been described.[11] With the patient in the supine position, the head is extended, with a pillow under the neck, and is turned slightly to one side. The thumb is used to administer slow but firm strokes up and down the artery over the sinus for a distance of 2 to 4 cm. Massaging should be done first on the right side and then on the left; both sides should never be stimulated simultaneously. The physician may listen to the heart while massage is carried out by having the patient hold the bell of the stethoscope over the apex. The procedure is terminated as soon as sinus rhythm recurs. In any event stimulation should be interrupted after a maximum of twenty seconds' continuous massage. The patient or a member of his family may be taught to use the technic in suitable cases. Askey[186] demonstrated that carotid-sinus stimulation in elderly patients may be hazardous because of the development of hemiplegia. Ventricular tachycardia[90] and ventricular fibrillation[91] have also been observed during vagal stimulation for paroxysmal atrial tachycardia.

Miscellaneous Measures

Most cardiac arrhythmias can be managed successfully by proper use of sedation, digitalis glucosides, quinidine, Pronestyl and carotid-sinus massage. Nevertheless, interesting reports concerning other antiarrhythmic agents have appeared in recent years. These reports are significant not because they apply to the routine care of the average arrhythmia but because they demonstrate that unusual therapy may succeed in exceptional cases in which the common antiarrhythmic measures have failed. Also, the hope always exists that a new class of more effective antiarrhythmic drugs may become established.

Youmans et al.[187] terminated supraventricular tachycardia by intravenous use of Neo-Synephrine, and Elek, Bernstein and Griffith[188] achieved the same result with methoxamine intravenously. It was postulated that these pressor drugs elicited cardioinhibitory reflexes from the aortic arch and carotid sinus besides exerting a direct cholinergic action. Cunningham and Schnitzker[36] reported success with Neo-Synephrine in the treatment of an infant with atrial tachycardia who had failed to respond to a variety of drugs, including acetylcholine. Berger and Rackliffe[189] found methoxamine especially effective.

Potassium has long been known to exert an antiarrhythmic effect, especially against the extrasystoles occurring from digitalis intoxication. This observation was recently confirmed by Enselberg et al.,[190]

who reported that potassium salts uniformly reduced or abolished digitalis-induced ventricular extrasystoles; they also used potassium salts successfully in a patient with bidirectional ventricular tachycardia and in 2 patients with atrial tachycardia resulting from digitalis intoxication. The relation between digitalis poisoning and potassium deficiency was further observed by Lown and his co-workers[35] in a group of patients presenting digitalis-induced atrial tachycardia with atrioventricular block that responded favorably to administration of potassium.

Other drugs of occasional value are the antihistaminics,[191, 192] Thevetoidin,[193] Nupercaine,[194] quinacrine,[195, 196] methacholine,[197] Dibenamine,[198] magnesium,[199] Dilantin[200, 201] and neostigmine.[202] Severe and frequent paroxysms of atrial fibrillation in a euthyroid patient have been eliminated by mild hypothyroidism produced with radioactive iodine. The arrhythmia had previously failed to respond to Pronestyl, quinidine and digitalis. In addition to these pharmacologic forms of therapy the surgical procedure of cervical sympathectomy has been reported to abolish supraventricular arrhythmias in some cases.[203]

Treatment of Cardiac Arrest

Drastic reduction or stoppage of cardiac output, commonly termed "cardiac arrest," may occur in a variety of conditions, including complete heart block with episodes of ventricular asystole, ventricular fibrillation and complete cardiac standstill. Management of these conditions has long presented a difficult problem. In recent years, fortunately, better differential diagnosis and pharmacologic advances have increased the effectiveness of medical therapy. Outstanding progress has also been reported in the treatment of cardiac arrest during surgery.

Stokes–Adams attacks resulting from ventricular standstill may be associated with complete heart block due to disease of the atrioventricular-conduction system or to carotid-sinus hypersensitivity. The treatment of choice is administration of epinephrine or related compounds. If attacks recur repeated injections of epinephrine or the longer-acting epinephrine-in-oil are required. Nathanson and Miller[204] demonstrated that episodes of ventricular asystole may be prevented by Isuprel in doses of 10 to 15 mg. sublingually or Paredrine in doses of 20 to 60 mg. orally at intervals of three or four hours. One case has been reported[128] in which ACTH overcame complete atrioventricular block with attacks of asystole that followed a posterior myocardial infarction. In this case the block evidently resulted from edema involving the conduction system rather than from actual pathologic interruption of the atrioventricular connection. In another case[128] attacks of asystole caused by extreme hypersensitivity of the carotid sinus ceased after the artificial production of mild hyperthyroidism by means of thyroid extract.

As noted earlier, Stokes–Adams attacks may occur as a result of paroxysmal ventricular fibrillation rather than asystole.[205] Since such attacks are extremely difficult to terminate therapy must be concerned chiefly with preventing the paroxysms of fibrillation. Schwartz et al.[108] have shown that atropine given intravenously in doses of 2 mg. is occasionally effective in aborting the Stokes–Adams attack. Isuprel and Paredrine may prevent episodes of ventricular fibrillation by accelerating the basic idioventricular rate.[206] Quinidine and Pronestyl are definitely contraindicated, since they have been known to induce ventricular fibrillation in the presence of complete heart block by depressing the basic idioventricular pacemaker.[207-209] In patients with previously normal atrioventricular conduction, on the other hand, Pronestyl or quinidine given intravenously is the treatment of choice for ventricular fibrillation.[208, 209] These drugs presumably eliminate the ventricular ectopic focus, enabling the impulse from the sinoatrial node to drive the ventricles and thereby restoring normal sinus rhythm as in the successful treatment of ventricular tachycardia.

Largely because of certain dramatic surgical procedures growing interest has been shown in the treatment of cardiac standstill and ventricular fibrillation. The background of these developments was recently described by Wiggers.[210] A review of 1200 cases by Stephenson, Reid and Hinton[211] revealed that the frequency of cardiac arrest during surgery has definitely increased in recent years. Three factors were held responsible: the expanding field of cardiac and thoracic surgery; the increasingly common practice of endoscopy and endotracheal intubation, cardiac catheterization and angiocardiography, all of which have reflex effects upon the heart; and the use of multiple drugs and anesthetic agents. Of these etiologic factors in cardiac arrest the vagovagal reflex accentuated by anoxia was considered most important.

Failure of the ventricles to eject blood, as a result of either standstill or fibrillation, requires immediate and drastic therapeutic measures. The cells of the brain may undergo irreparable damage unless cerebral circulation can be restored within three or four minutes. Direct cardiac massage may be life saving in either cardiac standstill or ventricular fibrillation.[212-216] The ideal rate of cardiac massage has not been determined. On the basis of volume-flow studies, Johnson and Kirby[217] advocated a rate of 80 to 120 a minute. Mean-femoral-pressure studies by Lape and Maison,[218] on the other hand, indicated an optimal rate of about 25 per minute. Venous return to the heart should be supplemented by rapid intravenous transfusion of blood. The patient is placed in the Trendelenburg position. Intermittent occlusion of the thoracic aorta is carried out to increase the blood flow to the brain and coronary arteries. When administered for

cardiac standstill massage should be continued for at least an hour unless spontaneous contractions are observed sooner. From 2 to 4 cc. of 10 per cent calcium chloride or 0.1 to 0.3 cc. of 1:1000 epinephrine in 5 cc. of physiologic saline solution may be injected into the left ventricle to augment the effect of massage.[219] In cases of ventricular fibrillation cardiac massage must be continued at least until the heart is well oxygenated. Injection of 5 cc. of 2 per cent procaine into the pericardial sac and intravenous administration of Pronestyl have been recommended. These measures alone, however, rarely convert ventricular fibrillation to normal sinus rhythm. As Kay[220] pointed out, the drugs merely make it more difficult if not impossible to restart the heart after asystole has been obtained. When oxygenation of the heart has been achieved by massage the electric defibrillator is the method of choice to abolish fibrillation.[221]

Many cases have been reported in which this technic was used with success. Cole[216] analyzed a series of 212 patients requiring cardiac massage during surgery; 110 survived. Since many of these patients presumably would have died without treatment, great credit is due the surgeons who devised present technics of direct cardiac massage. The study of Stephenson et al.[211] showed that failures were attributable to delay in treatment, injudicious use of drugs, lack of familiarity with proper methods of massage and absence of defibrillating equipment. In view of the rising incidence of cardiac arrest during surgery mortality might be reduced still further if continuous electrocardiograms or oscillograms were recorded routinely throughout cardiac and thoracic operations.

A most promising development in the treatment of cardiac arrest appears to lie in the introduction of artificial cardiac pacemakers.[222] Callaghan and Bigelow[223] successfully demonstrated the use of an electric artificial pacemaker in cardiac standstill. This apparatus requires direct application of the stimulating electrode to the heart. For more general use stimulators and defibrillators that could be applied to the unopened chest would be desirable. Zoll[224] has already reported success in restarting the heart in ventricular standstill with an external stimulator. He predicts that apparatus can be developed that will defibrillate a heart by external means and restart it with an external pulse generator.

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MEDICAL INTELLIGENCE

DOCTORS AFIELD

Louis Marshall

WILLIAM R. LAIRD, M.D.*

MONTGOMERY, WEST VIRGINIA

A LITTLE publicized but significant figure in the early history of the United States is Louis Marshall, the brother of John Marshall, United States Chief Justice. His contribution to education has been largely forgotten. He was, however, a pioneer in bringing into education the spirit of experiment, adventure and the belief that the educative process should promote growth by developing natural instincts rather than suppressing them. It was not until 1900 that this idea, long prevalent in elementary education, began to spread among the colleges.

The programs of the University of Chicago, St. John's College, Rollins College, the University of Wisconsin, Sarah Lawrence College and others have attracted wide attention. Few people realize that long before these institutions were evolving an experimental program and many years before Dr. Harper's experiment in Chicago, some striking innovations were being made at Washington College, now Washington and Lee University, under the guidance of Marshall.

The Marshall background is interesting. He was one of fifteen children, all of whom survived to maturity, and three of whom — John, James and Lewis, as he had been christened — achieved distinction. His father, Thomas Marshall, was a "man of parts," who after serving with distinction in the American Revolution settled permanently in Kentucky, acquired large holdings, and became prominent in public affairs. On his death he left Buckpond, the estate on which he had settled, to his son, Louis.

The family history on the mother's side was also one of eminence, making him kin to Thomas Jefferson, Robert E. Lee and several distinguished

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Randolphs. Lewis Marshall was born in Fauquier County, Virginia. The birthplace is still standing as part of a larger dwelling, Oak Hill, built later by Thomas Marshall, a son of John Marshall.

His early education at Buckpond, where the family had moved from Virginia, was supervised by his father and by Scottish tutors. Then after a year in Philadelphia he went to Edinburgh and Paris to study medicine. In France he changed his given name of Lewis to Louis and became an agnostic. He was imprisoned during the French Revolution and was in danger of being executed, but was released through the efforts of his brothers, John and James.

Education interested him more than medicine after his return to America and subsequent marriage, and in the early 1800's he established a classical school for boys at Buckpond. Some of the graduates became famous in later life. For this reason, and also because of its strict discipline and high standards, the school attracted considerable attention.

When in 1830 he became president of Washington College a curious transformation took place in his character. He became a thorough-going radical in his educational ideas, but a conservative in religious opinions. He gave up his agnostic views and was for many years an elder in the Presbyterian Church.

At Washington College he abandoned his ideas about strictness of drill and discipline and went to the opposite extreme. No class instruction was given unless some group requested it, but individuals came as each one desired to recite to the instructor or to obtain help. He carried out with college students the principles Froebel years before had advocated for children. The young men were to be completely uninhibited and unhampered in their search for knowledge.

His way as a reformer was difficult and aroused bitter opposition on the part of his faculty, who thought that chaos had come indeed. But for a time he was the hero of his students. His classroom was fitted with an armchair and a bed, and he received his students while lounging comfortably, pipe in mouth. Sometimes, instruction was given outdoors by starlight. He evidently agreed with Kant's belief, "Two things fill me with awe; the starry heavens above, and the moral law within." He might have had complete success in his experiment if he had known how to temper educational adventure with prudence. Unfortunately, he carried the informality of instruction into recreation, and in the realm of play his students took advantage of him and became unduly familiar. When he tried to reprimand them, often in a sarcastic manner, he lost control of the situation.

Naturally, the faculty, which had never given him cordial support, rejoiced. Having lost the approval of his students and being unable to stem the tide of opposition from the faculty, he set out for Kentucky in 1834 and resumed teaching. In 1838 he was made professor of languages at Transylvania University and for two years was acting president.

It is characteristic of such a strong-minded individualist that spectacular changes of opinion should have occurred. The shift from agnosticism to orthodoxy is perhaps more understandable than the switch from conventional educational severity to experimental liberalism. Renouncing this liberal program for severity seems highly inconsistent. If he truly believed in his system, there were far better ways to attempt a correction of its faults than the use of sarcasm and ridicule.

Inconsistency was evidently a fundamental trait of his character. In spite of his Virginian background — his father at one time had owned 22 slaves — he was a Unionist. Quite typically, he seems later to have entertained some qualms of doubt about this position. But he was a man of outstanding intellect and force of character in spite of his inconsistencies. He was sincere to the point of fanaticism, eccentric in manner and opinion and impatient of opposition. In his later life he became an assiduous Bible scholar, especially of the prophets, whom he expounded to his students with great fervor. He was even so rash as to set the date when the world was to be destroyed.

His pronounced opinions provoked not only philosophic debates but also actual quarrels. Throughout his life he carried scars from duels fought in France. Unfortunately, few properly authenticated facts exist besides the ones related above. Much documentation has been destroyed by fire. The house at Buckpond is no longer standing, but relatives living nearby have an oil painting of Marshall.

It detracts nothing from the glory of Dr. Harper that sixty-two years before his time a similar experiment was conducted at what is now Washington and Lee University. It is interesting to speculate how close Marshall may have come to succeeding in an undertaking so revolutionary.

> The little more, and how much it is;
> The little less, and what worlds away.

Many stars are bright in the crown of Washington and Lee University. In this constellation Dr. Louis Marshall is by no means one of merely second magnitude. Thanks to him, his university may be proud of having conducted a significant educational experiment long before such education became respectable.

The pioneer who is first to explore new territory deserves special recognition. His successors may travel faster and farther, but to him belongs the peculiar glory of having been the first to enter the unknown land and enlarge the boundaries of human heritage.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*
VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40131

PRESENTATION OF CASE

A fifty-two-year-old housewife entered the hospital because of the sudden onset of abdominal pain.

Shortly after breakfast on the previous day the patient was making a bed when she experienced sudden, sharp pain in the lower middle portion of the abdomen that caused her to double up. The pain quickly spread and became notably severe in a ring around the abdomen and back at the level of the umbilicus. Although it varied somewhat in intensity, it was not crampy and remained constantly present for the next forty hours until admission. The pain was somewhat relieved when she sat up and made worse when she lay down. An hour and a half after the onset she vomited her breakfast, and was slightly relieved. Thereafter, she was unable to eat because of persistent anorexia and gaseous eructations. She took an enema, which had no results and gave no relief from the pain.

For many years she had had chronic constipation, with bowel movements once or twice a week after laxatives. Chronic indigestion, belching after meals and occasional vomiting had been present infrequently although these symptoms were somewhat worse in recent months. The patient denied intolerance to fatty foods, jaundice or hematemesis. She also denied previous episodes of similar abdominal pain although she had had some abdominal pain and distention in connection with a "nervous breakdown" four years previously. Appendectomy and hysterectomy had been performed twenty-four and twenty-two years before admission.

Physical examination showed a woman who appeared to be in severe pain, complaining of tenderness over the entire abdomen. The pupils, which were small and round, reacted sluggishly to light and on accommodation. Examination of the heart and lungs was negative. The abdomen was not distended. Tenderness was moderate in degree on palpation throughout the abdomen but most severe in the right lower quadrant; there was no rebound or flank tenderness. Some muscle spasm in the right and left lower portions of the abdomen was believed to be voluntary. Peristalsis was normal, and no organs or masses were palpated. Rectal and pelvic examinations were negative.

The temperature was 99.8°F. by rectum, the pulse 60, and the respirations 20. The blood pressure was 130 systolic, 70 diastolic.

Urinalysis was negative. Blood studies revealed a hemoglobin of 13.8 gm. per 100 cc. and a white-cell count of 14,200, with 84 per cent neutrophils. The serum sodium was 132 milliequiv., the chloride 100 milliequiv., and the carbon dioxide 16.0 milliequiv. per liter; the nonprotein nitrogen was 26 mg., the amylase 73 units (normal, 15 to 45 units per 100 cc.), the alkaline phosphatase 2.9 units, and the bilirubin 0.4 mg. per 100 cc. Cephalin flocculation was negative in forty-eight hours, and the prothrombin time normal. Sigmoidoscopic examination disclosed no mucosal lesions; however, dark-red and brown liquid material was seen to come from above and this gave a +++ test for occult blood. Roentgenograms of the abdomen showed gas in the transverse and descending colon and feces in the cecum. There was no free air and no small-bowel gas. A homogeneous soft-tissue density in the pelvis suggested a somewhat enlarged uterus. A barium enema filled the colon, with no evidence of obstruction.

In the hospital, the patient was observed and treated with sedation and intravenous infusion of fluids. Drowsiness was the most prominent symptom. A neurologist was unable to find evidence of a focal neurologic lesion and suggested that the drowsiness might be due to previous medication. At the end of twenty-four hours she appeared about the same as before although the abdomen was slightly more tense and still tender to deep palpation in both lower quadrants. Peristalsis was subdued but present. The temperature was 99°F., and the pulse 90; the white-cell count was 13,800, with 91 per cent neutrophils. A serum amylase determination on this day was 48 units per 100 cc.; the lipase was 0.6 cc. (normal, under 2 cc.). Twelve hours later she appeared pale and sweaty, with a weak pulse; an abdominal fluid wave had developed. A second white-cell count was 24,800, with 96 per cent neutrophils. A diagnostic abdominal paracentesis was performed, and bloody serous fluid recovered. This fluid had a specific gravity of 1.018 and contained many red cells but few white cells. About two hours later an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. GRANT V. RODKEY*: The sudden onset and rapid progression of symptoms and signs in this case certainly indicate that this was an acute abdominal emergency that was an entity in itself and not related to some more generalized disease. The evidence in the protocol suggests that extensive tissue damage was associated with whatever process was present. This was manifested by derangement of

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electrolytes, high white-cell count, with a high percentage of neutrophils, and the rapid development of a bloody peritoneal exudate. As one reads over the protocol, there is an inescapable suggestion that some organ may have become obstructed or infarcted, with progressive tissue damage and sudden rupture into the abdominal cavity. I am not sure that I can justify this suspicion, but it is suggested by the course of the patient's illness.

May I see the x-ray films?

DR. JOHN F. GIBBONS: In the films of the abdomen, all of which were taken on the same day, in the supine and erect positions, gas is seen in the large bowel all the way around except in the area of the right colon that is filled with a lot of fecal material; there are a couple of loops of gas-filled but nondistended small intestine in the left side of the midabdomen. There is no free air under the diaphragm in the erect position. The density in the pelvis was said to be suggestive of an enlarged uterus; since we know that the patient had had a hysterectomy, I think the shadow suggests the presence of fluid in the pelvic peritoneal cavity or a distended urinary bladder. Indicative of fluid in the remainder of the abdomen is the fact that the loops of large bowel and small bowel are separated more than they normally are. There are no abnormal soft-tissue masses and no unusual calcifications. The findings suggest the presence of fluid in the peritoneal cavity and some degree of ileus, without mechanical bowel obstruction.

DR. RODKEY: It is true that the barium-enema examination was negative?

DR. GIBBONS: Yes; the colon was quite normal in all respects.

DR. RODKEY: It seems to me that the way to approach this problem is to list the many possible conditions and rule out those that seem unlikely. A number of conditions that cause acute abdominal emergencies may be mentioned only to be dismissed. Among those are renal or ureteral calculus, dissecting aortic aneurysm, acute large-bowel obstruction, diverticulitis of the sigmoid or cecum, with perforation, volvulus, intussusception and acute appendicitis, which occasionally arises in the stump of a previously amputated appendix. Recently, I have seen a case of an intraperitoneal rupture of a urinary bladder that produced signs and symptoms surprisingly like those in this case so that I include that as a condition that I think was not present.

Among the causes of abdominal emergencies that I do not believe were present here but must be considered more carefully is acute small-bowel obstruction. The onset and character of the pain — although it was not described as crampy after it had become manifest — are perhaps consistent with that diagnosis. It would be quite unusual for an acute small-bowel obstruction to have been present without more x-ray evidence, although an obstruction fairly high in the small bowel may not show distended, gas-filled loops above that level. Possible causes for acute small-bowel obstruction in this case are the facts that the patient had had previous operations and may have had adhesions or an internal hernia in one of the natural orifices of the abdomen, but no mention was made of that. I do not believe that acute small-bowel obstruction is a likely diagnosis in this case.

A twisted ovarian cyst would produce many of the symptoms and signs that were present — especially if the cyst had become gangrenous and ruptured. Moreover, it would explain the presence of a mass in the pelvis noted in the x-ray films. I should think that such a mass would have been noted on pelvic or rectal examination, although that is not necessarily true. The one consideration in the protocol that deters me from accepting this diagnosis is the finding of guaiac-positive fecal material on sigmoidoscopic examination. I do not think a perforated, gangrenous ovarian cyst fits into that picture.

One must consider mesenteric embolus, with infarction of the small bowel, or mesenteric thrombosis. We have no reason to suppose from the protocol that she had an abnormal heart, and embolism to the the mesentery is therefore unlikely. Thrombosis in this age group is also unlikely. I might say in passing that the presence of peristaltic sounds throughout the course of the illness is not completely against this diagnosis, because peristalsis is occasionally present even when a portion of the bowel is gangrenous. Mesenteric thrombosis would explain the presence of guaiac-positive stools and would fit well with the final few hours of the patient's course. If this had been the diagnosis, one would have expected a higher white-cell count on the day of admission. This is an important point, and, although I cannot rule it out, I do not believe mesenteric thrombosis was present here.

A group of conditions that are difficult or impossible to exclude in this case are those related to the biliary and upper intestinal tracts. Did the patient have acute cholecystitis, perhaps with gangrene and perforation? No stones were seen on the x-ray films, but that does not give me a lead one way or the other. The past history of chronic indigestion is consistent with cholecystitis as the underlying cause. I should say that the history and the manner of onset and distribution of the pain were not quite in keeping with acute cholecystitis. However, we see enough variation in the characteristic symptoms of that disease to know that these could occur with cholecystitis. Furthermore, when the liver is large or the gall bladder low — I did not think the liver appeared enlarged on the film, and Dr. Gibbons confirmed this — maximum tenderness from acute cholecystitis is sometimes present in the right lower quadrant. The guaiac-positive stool I can hardly explain by this diagnosis — it may occur, perhaps, if

a stone goes through the common duct. I do not believe the diagnosis was acute cholecystitis.

Perforated duodenal or gastric ulcer has to be considered. The past history, again, is consistent with the presence of such lesions. There was no free air under the diaphragm, which one expects to be present in approximately three fourths of the cases forty hours after the perforation. No pain in the shoulders was mentioned, but the absence of such a pain is not significant. The findings on abdominal examination and the clinical and laboratory findings are all consistent with a perforated ulcer. The bloody serous fluid recovered on paracentesis gives me a little pause. It might occur, but I do not recall having seen that type of fluid in any laparotomy that I have ever done for a perforated duodenal or gastric ulcer. Besides, I do not think the distribution of the pain was quite in keeping with a perforated ulcer.

The level of the pain about the umbilicus has served to turn my attention to the lower small bowel, which brings up the next possibility — a Meckel diverticulum. An ulcer in a Meckel diverticulum might explain the past history of occasional indigestion and the previous episode of abdominal pain. Perhaps an ulcer in a Meckel diverticulum bled, giving an adequate explanation for the guaiac-positive fecal material. Such an ulcer might have progressed to perforation, and bleeding of the ulcer could have contributed to the bloody serous fluid. On the other hand, perhaps a fecalith in a Meckel diverticulum obstructed the bowel and led to infarction and gangrene, with perforation. I cannot rule out the diagnosis of some disease within a Meckel diverticulum, either a bleeding ulcer with perforation or obstruction and infarction with perforation. I think that either possibility is consistent with every feature of the case.

Another possibility is acute pancreatitis. There was no calcification in the head of the pancreas so far as we can see in the films. If such a calcification had been present, it might have been helpful; that it was not means nothing. The onset of pain in pancreatitis is often sudden, as in this case. The distribution of the pain and tenderness is consistent with acute pancreatitis, although I should have expected more tenderness in the epigastrium and a little less in the lower abdomen. That is not always true, because digestive ferments and irritative exudates tend to leak through the foramen of Winslow and gravitate into the right gutter, causing maximum tenderness in the right lower quadrant. The amylase and the lipase determinations are something that I might next consider. The serum amylase was moderately elevated, but this is not a helpful level. It is at about the level often observed in cases of perforated ulcer, intestinal obstruction, peritonitis, acute parotitis and even, occasionally, cerebral trauma.[1] On the other hand, in many cases of proved acute pancreatitis, the serum amylase is within this range. In a recent series of cases of acute pancreatitis reported from this hospital by Raker and Bartlett[2] the serum amylase ranged from 26 to 238 units per 100 cc. The lipase determination was normal. We know that the amylase tends to rise quickly during the first day or two and then falls after the pancreatitis becomes established, whereas the lipase elevation is more likely to be delayed for twenty-four hours and then to persist longer. Perhaps this patient was caught in the phase where the serum amylase was falling and the lipase had not yet become established. It might have been helpful if the serum calcium had been studied, since we know that its level sometimes falls in acute pancreatitis. However, I do not believe that there was a significant lowering of the calcium level because drowsiness was mentioned as a prominent symptom. In summary, many signs of the case are consistent with acute pancreatitis. However, I am not so sure that this is as likely a diagnosis as some disease within a Meckel diverticulum.

To sum up the case, a number of diagnoses that I cannot exclude have to do with necrotizing processes in the abdomen. I think that obstruction or infarction of a hollow viscus, with subsequent perforation of the organ, seems to fit the picture better than any other concept, and I believe that the patient may have had some complication of a Meckel diverticulum. I do not believe small-bowel obstruction was present although I cannot rule it out. Mesenteric thrombosis or embolism, similarly, I cannot rule out. On the basis of statistics, I should prefer to make a diagnosis of acute pancreatitis rather than perforation of a Meckel diverticulum, but pancreatitis does not seem to fit as well in this case.

Dr. David S. Kahn: Dr. Peete, will you tell us your impression preoperatively and your findings at operation?

Dr. William P. J. Peete: I wish we had had Dr. Rodkey on the Surgical Service last year when the patient was on the ward because this was one of our more difficult abdominal problems. He made the important initial diagnosis: acute abdominal emergency. There are always features that can never be brought out in the protocol; one of these was that this woman was quite hyper-reactive. Her reactions suggested hysteria. Shortly after admission she was found to have a distended bladder, and she was catheterized, with temporary but complete relief of symptoms. Therefore, for a time, we were not sure about the diagnosis of acute abdominal disease. Our initial impression, nevertheless, was acute pancreatitis, and because she had previously had abdominal surgery, a small-bowel obstruction, with a question of strangulation, was the diagnosis for which we sought evidence. The white-cell count twelve hours after admission was lower than the first one. She had an initial amylase of 73 units, which dropped to 48 units per 100 cc. The abdomen was flat, and she passed gas by rectum. Peristalsis was

normal. These findings confused us about the situation during the first thirty-six hours in the hospital. One striking observation was that she not only had severe pain during periods when she awakened from drowsiness but also had voluminous gaseous eructations. We watched her closely and examined the abdomen every hour or so. There was never localized tenderness. When the white-cell count was found to be 26,000 she had also been judged to have fluid in the abdomen. At that point we made the diagnosis of acute abdominal emergency, — strangulation obstruction of the small bowel, — but thought we might find acute pancreatitis.

Clinical Diagnosis

Strangulation obstruction of small bowel.
?Acute pancreatitis.

Dr. Grant V. Rodkey's Diagnosis

Meckel's diverticulum, containing fecalith, with obstruction, gangrene and perforation.

Anatomical Diagnosis

Strangulated small bowel caused by adhesive band.

Pathological Discussion

Dr. Peete: Operation disclosed a strangulation obstruction of about 240 cm. of small-bowel loops of terminal ileum caught under an adhesive band extending from the apex of the vaginal cuff to the upper edge of the old abdominal incision.

Dr. Kahn: The resected specimen of ileum measured 160 cm. in length. Microscopical examination confirmed the surgical impression of early hemorrhagic infarction of the bowel.

Dr. Peete: This case emphasizes the obscure nature that strangulation obstruction assumes upon occasion: it occurred without distention, abnormal peristalsis, localized tenderness, fever or diagnostic x-ray findings, with at first minimal and then less leukocytosis, with the passage of gas by rectum and in a woman whose demeanor led one to think about psychiatric disease. In retrospect we recognized that we erred in not operating earlier because we were lulled by apparent improvement and what appeared to be abnormal psychic reactions, and because we did not recognize massive belching for what it was. Indeed, the unusual and persistent abdominal pain with variable tenderness, the leukocytosis and the prior operations did warrant earlier laparotomy.

Dr. Allan M. Butler: What happened to the patient postoperatively?

Dr. Peete: She made an uneventful recovery, and six weeks after operation, when she returned for follow-up examination, she was perfectly well.

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CASE 40132

Presentation of Case

A forty-three-year-old man entered the hospital because of joint pains and dyspnea.

The patient at the age of four years had migratory joint pains shortly after an episode of tonsillitis. The joints became swollen, red and hot. Practically every winter thereafter he had similar attacks of joint pains. At fourteen years and again at twenty-six years of age he was immobilized in bed for six months and two years respectively because of severe pain in all the joints. Thirteen years before admission nonpainful, swollen ankles first developed. Seven years later he again had severe joint pains and was admitted to another hospital, where he received 95 injections of penicillin, with some improvement in his condition. During the next five years he remained reasonably well, worked full time and had only moderate attacks of joint pains with swelling each winter. One and a half years before admission shortness of breath developed, and he first noted "skipping of the heart." Exertion led to such severe shortness of breath that he had to stop and gasp for breath. He was digitalized by his physician, improved in two or three weeks and ceased taking digitalis. From then on, whenever he had an attack of shortness of breath, he took one or two pills of digitalis at intervals until he got relief and then stopped the drug. The dyspnea progressed and became so disabling that he was forced to give up most of his work about four and a half months before admission. Orthopnea developed and progressed to the point where he had to sleep in a chair. He was digitalized again, continued on the drug for the next two or three months, improved considerably and felt well. Approximately a month before admission the dyspnea became increasingly severe, and the orthopnea and palpitations increased. He began to

perspire profusely, requiring frequent changes of clothing. The digitalis had only a mild effect on the symptoms. A week before admission he had watery diarrhea for three days, with twelve movements daily. After this he became anorectic and began to vomit, and the digitalis was stopped. During the day before entry the dyspnea became more severe; ankle edema appeared, progressed rapidly throughout the day and was most prominent in the right leg, which became hot, tender, red and painful. For a few days he had had a nonproductive cough. There was no history of chest pain, pleurisy, sputum, hemoptysis, petechiae or epistaxes. A few days before admission he was told that the scleras were yellow. For six months, up until two weeks before entry, he had been receiving prophylactic injections of penicillin.

Physical examination revealed a severely dyspneic, ill man who was sitting up in bed and sweating profusely. The eyes were prominent. Both pupils were dilated. The scleras were icteric. The superficial neck veins were dilated and pulsating. A few crackles were heard at both lung bases — more on the right than the left.

The heart was enlarged to both sides; the maximal apical intensity was felt 13 cm. to the left of the midline; the right border of the heart was 7 cm. from the midpoint of the sternum in the fifth intercostal space. There was an aortic systolic thrill, as well as a Grade 4, harsh, systolic murmur, which was transmitted over both sides of the thorax, and a Grade 3, aortic, diastolic murmur, best heard along the left sternal border but well transmitted to the apex. A high-pitched, shrill systolic murmur was heard at the lower end of the right sternal border. The heart sounds were tumultuous and banging; the pulmonic second sound was absent. A tender liver edge was palpated 4 fingerbreadths below the right costal margin. The spleen was not felt. There was ++ edema of the left ankle and ++++ edema of the right; there was edema of the right leg to the knee, and the calf was hard and tender. There was a positive Homans sign in this leg.

The temperature was 102°F., the pulse 100, and the respirations 30. The blood pressure was 130 systolic, 60 diastolic.

The urine gave a +++ reaction for albumin and a +++ reaction for bile; the sediment contained 6 to 8 white cells and 1 or 2 cellular and coarse granular casts per high-power field. Examination of the blood showed a hemoglobin of 17 gm. and a white-cell count of 20,500, with 76 per cent neutrophils. The sodium was 126 milliequiv., the potassium 5 milliequiv., and the chloride 86 milliequiv. per liter; the nonprotein nitrogen was 76 mg., the bilirubin 2.2 mg. direct and 3.5 mg. total, the alkaline phosphatase 3.8 units, and the total protein 6.1 gm. per 100 cc. The prothrombin time was 18 seconds (normal, 14 seconds). A blood Hinton test was negative. Blood cultures demonstrated no growth. A stool gave a negative guaiac reaction. An electrocardiogram disclosed atrial fibrillation at a rate of 75, a QRS interval of 0.10 second, normal voltage and a tendency to left-axis deviation. The ST segments were sagging and the T waves diphasic in Leads 1, 2, aVL, aVF, V_5 and V_6; the R waves were moderately tall in Leads V_5 and V_6. Roentgenograms of the chest revealed great enlargement of the heart shadow; both ventricles and probably the left atrium were enlarged. The hilar and pulmonary vascular shadows were increased in prominence. In the x-ray films the tip of the liver overlay the iliac crest.

The patient responded poorly to treatment with oxygen, penicillin, theocalcin, anticoagulants, salicylates and digitalis. He continued to have an elevated temperature, severe dyspnea, profound asthenia and profuse sweats. On the third day the digitalis was stopped because of bigeminal rhythm. On the fourth day he coughed up bright-red blood and a constant pain in the left anterior axilla later developed that was aggravated by deep inspiration; physical examination revealed a distinct rub in this region, and an x-ray film of the chest showed the hilar and pulmonary vascular shadows to be more prominent, with a hazy, cloudy density throughout both lung fields, particularly the left, and a more dense area in the lingula of the left upper lobe (Fig. 1). He improved somewhat after this episode, but on the seventh day pain along the right costal margin and then mild epistaxis developed. He became cyanotic, with gasping respirations, and died shortly thereafter.

Differential Diagnosis

Dr. H. Walter Jones, Jr.*: The chain of events that led to the death of this forty-three-year-old man began at the age of four, when migratory polyarthritis followed an attack of tonsillitis. Many, and often severe, recurrences of the joint symptoms were

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noted during the ensuing years. Nevertheless, the physical examination at the time of the terminal illness apparently did not reveal any objective joint changes. Consequently, I think that the joint disorder was rheumatic fever rather than rheumatoid arthritis and that it led to rheumatic heart disease, atrial fibrillation and congestive heart failure.

May we see the x-ray films?

DR. JOHN F. GIBBONS: The first films of the chest show marked cardiac enlargement apparently involving all chambers (Fig. 1). The cardiothoracic ratio measures 21.4:31.5 cm. There is slight widening of the vascular shadows at the lung roots. The peripheral lungs are clear, and there is no evidence of effusion.

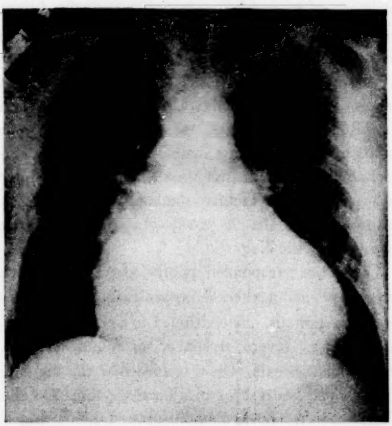

FIGURE 1. *Initial Roentgenogram of the Chest, Showing Marked Cardiac Enlargement and Prominent Vesssels in the Upper Portions of the Lung Fields.*

Survey films of the abdomen taken at the same time demonstrate considerable enlargement of the liver but no abnormalities otherwise.

Films of the chest taken four days later reveal that mottled densities have appeared in both lungs, suggesting the presence of pulmonary edema. Behind the left heart shadow in the region of the lingula of the left lung there is a vaguely defined area of increased density, which suggests the possibility of a pulmonary infarct or superimposed pneumonia. There is still no free fluid, and the heart is not changed significantly in size. The pulmonary vessels are more engorged at this time.

DR. JONES: Let us consider the cardiac lesions more specifically. The systolic thrill in the aortic area and the loud aortic systolic and diastolic murmurs indicate aortic stenosis and insufficiency. The electrocardiographic abnormalities are those associated with hypertrophy of the left ventricle and are consistent with disease of the aortic valve. The presence of atrial fibrillation leads me to suspect mitral stenosis as well. I hesitate to make this diagnosis in the absence of a rumbling apical diastolic murmur although I know that the presystolic component of the murmur is masked by fibrillation. Dr. Morgan, was there any disagreement about the description of the heart murmurs?

DR. WINFIELD S. MORGAN: One observer did report a Grade 1 diastolic rumble at the apex. He also said that the systolic murmur at the apex was distinct from the aortic one.

DR. JONES: I believe, then, that this patient had mitral stenosis and insufficiency. In addition the systolic murmur heard at the lower end of the right sternal border suggests tricuspid insufficiency. Relative tricuspid insufficiency is common in heart failure, but organic tricuspid disease is difficult to diagnose since it is almost never a pure lesion. One final point that troubles me in the description of the heart sounds is the absent pulmonic second sound, which would be very unusual with mitral stenosis. I wonder if the picture was complicated by a congenital lesion such as pulmonic stenosis, but I cannot be sure.

A month before admission to the hospital the patient began to perspire profusely, and his congestive heart failure became refractory to treatment. One immediately thinks of subacute bacterial endocarditis, but subsequent blood cultures were negative, the spleen was not enlarged, there were no petechiae, and there were no red cells in the urine. Hyperthyroidism would account for the sweats and poor response to digitalis but not for the fever. A recurrence of active rheumatic fever is another possibility. The clinicians evidently suspected rheumatic fever since he was treated with salicylates. Theoretically, the penicillin therapy during the six months before admission should have prevented a rheumatic flare-up. However, we know now from biopsies obtained during cardiac surgery that histologic evidence of rheumatic activity may persist long after the clinical

signs are quiescent. I doubt if rheumatic activity was of clinical significance in this case.

We come finally to the condition that I think was responsible for this patient's terminal illness — namely, multiple pulmonary emboli. He had atrial fibrillation, and, on the day before admission, thrombophlebitis developed in the right leg. He may well have had a silent phlebothrombosis in the other leg; thus, he had an ample source of emboli. He was jaundiced, and we know that jaundice may occur with pulmonary infarction and congestive heart failure. The poor response to cardiac treatment in the hospital would be expected if further emboli were being thrown off. The films of the chest taken four days after admission show an area of increased density in the lingula of the left upper lobe that I take to be a pulmonary infarct. The patient was given Dicumarol in spite of the impaired liver function, and he may have been overtreated since an episode of hemoptysis occurred on the fourth day. Finally, on the seventh day pain along the right costal margin and increasing cyanosis signaled what was probably a terminal pulmonary embolus.

My final diagnoses, then, are rheumatic heart disease, with aortic stenosis and insufficiency, mitral stenosis and insufficiency, atrial fibrillation, congestive heart failure, chronic passive congestion of the liver, thrombophlebitis of the right leg and multiple pulmonary emboli and infarcts.

Clinical Diagnoses

Emboli, with infarction of lung, lingula of left upper lobe.
Thrombophlebitis.
Rheumatic heart disease, with aortic stenosis.

Dr. H. Walter Jones's Diagnoses

Rheumatic heart disease, with aortic stenosis and insufficiency, mitral stenosis and insufficiency, atrial fibrillation, congestive heart failure, and chronic passive congestion of liver.
Thrombophlebitis, right leg.
Multiple pulmonary emboli and infarcts.

Anatomical Diagnoses

Rheumatic heart disease, with severe aortic and mitral stenosis.
Cardiac hypertrophy and dilatation, marked (weight, 900 gm.).
Pulmonary infarcts.
?Rheumatic pneumonitis.
Thrombophlebitis, leg veins.
Chronic passive congestion, generalized.
Jaundice.
Mural thrombus, left atrial appendage.
Pericarditis, healed.

Pathological Discussion

Dr. Morgan: The clinicians who followed this patient on the ward agreed with Dr. Jones that the patient had rheumatic heart disease with aortic stenosis and insufficiency but believed that the mitral lesion was chiefly one of insufficiency, with only questionable stenosis. They also raised the possibility of tricuspid stenosis, and they believed that he actually had active rheumatic fever at the time of death. At autopsy the heart was very large, weighing 900 gm. Both ventricles and the left atrium were greatly dilated, and there was hypertrophy of both the right and the left ventricle. The pulmonary and tricuspid valves were normal, but the aortic and mitral valves showed severe, old rheumatic involvement, with calcification, fixation and stenosis. There was no evidence of active rheumatic endocarditis or subacute bacterial endocarditis. A mural thrombus was present in the left atrial appendage. The lungs were markedly congested and edematous, weighing almost 2000 gm. Microscopical examination demonstrated extensive hyaline membrane formation lining alveoli and large air sacs. This process has been interpreted by some as evidence of active rheumatic disease, and it has been called "rheumatic pneumonia." It is not considered to be a specific reaction, however, and sections of the heart did not reveal Aschoff bodies or other stigmas of active rheumatic fever. The pulmonary artery contained multiple small emboli, and there were corresponding pulmonary infarcts, the largest measuring 4 cm. in greatest dimension. Most of the infarcts appeared to be of one or two weeks' duration and probably accounted for the white-cell count of 20,000 noted on admission and maintained throughout the hospital stay. Thrombi were found in the leg veins bilaterally, and presumably these were the source of the pulmonary emboli. The liver and spleen were severely congested. I think it most probable that the jaundice noted clinically was, as Dr. Jones suggested, due to the pulmonary infarcts; the central congestion of the liver was severe but no more so than we see in many cases without jaundice. The kidneys were grossly and microscopically normal except for congestion, and it is possible that the albuminuria was on that basis.

The New England Journal of Medicine

Official Organ of
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THIRTEENTH CONFERENCE ON CHEMOTHERAPY OF TUBERCULOSIS

THE success that antibiotics have achieved in many infections has led to their use in a variety of diseases and under conditions in which their value has never been proved. Indeed, there appears to be a driving impulse within a large segment of the medical profession to give some antimicrobial agent to every patient with fever or with the least suspicion of infection, irrespective of the need or the desirability for doing so, and often without regard to the potential harm that might be done. This general philosophy, which is being carried over into other fields of therapy, seems to be permeating present-day medical practice and teaching and threatens to undermine the scientific structure of medical practice.

Whatever the educational, social or economic background for this undesirable trend it is pleasing to know that at least some counteracting forces are working toward the development of a more rational use of therapeutic resources. Among the most effective and fruitful of these forces have been the Conferences on Chemotherapy of Tuberculosis sponsored by the Veterans Administration with the collaboration of some Army and Navy hospitals. At the thirteenth of these conferences, held in St. Louis, February 8-11, 1954, the findings and deliberations maintained the high standard of performance set by its predecessors.

In the keynote address Dr. William B. Tucker discussed the history of concurrently controlled cases in studies on the chemotherapy of tuberculosis as part of the Veterans Administration's programs. Random selection of cases for comparison of results of different types of therapy, which had been used first on a large scale by the Medical Research Council of Great Britain and also by the United States Public Health Service, has now been employed with great effect for several years by the 50 collaborating hospitals. The morality of this type of clinical study was first criticized as doing violence to the conscience of the participating physicians and often conflicting with their clinical judgment. It was apparent, however, that the criteria of individual judgment and conscience were not always sound, and the results of their application in practice did not always stand the test of scientific analysis. By sufficient knowledge about the important factors in a disease, by uniform objectives and the same types of observations in large numbers of cases it eventually becomes possible to correlate the background factors and to learn the best treatment as well as the conditions under which any particular type is superior. This eliminates errors resulting from bias and from preconceived notions or from the erroneous extension of conclusions that are not always warranted.

The wisdom of this laborious method of collecting and analyzing carefully controlled data was well illustrated at this conference by a report from one of the large Army hospitals on a study of the efficacy of the combined use of streptomycin, para-aminosalicylic acid (PAS) and isoniazid. This

study was done without random selection of cases for comparison with other regimens. The effects in a series of consecutive cases were analyzed and then compared with experiences at the same hospital during the preceding months. As it turned out, the results of the use of all three agents, contrary to expectation, were definitely inferior to those obtained with combinations of streptomycin with either PAS or isoniazid. Analysis of the background factors indicated that the last series, which comprised patients treated with all three drugs simultaneously, included more chronic and severe cases with large cavities, in which favorable results are much less frequently achieved.

Of course, if the efficacy of the triple regimen had turned out to be superior in spite of the less favorable factors, these investigators might have considered themselves vindicated in their use of the consecutive-case method for study; the objectives of the study were not achieved, and the time and energy expended served only to add confusion. Fortunately, the majority of hospitals participating in this conference are co-operating in the random study, from which it should be possible to evaluate the comparative efficacy of these regimens when a sufficient number of cases have been treated and followed long enough.

Details of the reports and discussions presented at this conference will eventually appear in its transactions; a few of the highlights may be mentioned briefly.

It was reported that tubercle bacilli that have become resistant to isoniazid during treatment with this agent nevertheless maintain their ability to produce progressive disease in patients. This is contrary to what might have been expected, since many observers have found that these organisms lose their virulence for guinea pigs.

Another group of investigators, using improved technics, grew virulent tubercle bacilli from the resected lesions of about two thirds of the patients who had received prolonged chemotherapy. This was of interest in comparison with the results reported by previous workers, who were able to see organisms in sections of resected lesions but could not culture the bacilli or produce lesions in guinea pigs with the resected tissues. Thus, it appears that many of these lesions contain organisms that are neither dead nor sterile, in the sense that they cannot multiply. The reasons for the differences in results remain to be worked out.

Remarkable effects were reported in the treatment of miliary and meningeal tuberculosis since isoniazid was added to the previous regimen of streptomycin and PAS. More than 80 per cent of patients with tuberculous meningitis and over 90 per cent of those with miliary tuberculosis treated with the triple regimen survived for twelve to eighteen months. Among patients in whom meningitis first appeared after treatment for the miliary disease about 40 per cent survived, in contrast to less than 20 per cent under earlier regimens.

The possibility of rapidly eradicating tuberculous infection was suggested in a report on the use of a combination of pyrazinamide and isoniazid in mice. The early results of a regimen employing this pair of agents in patients with advanced pulmonary tuberculosis appear to have been far superior to those obtained in comparable cases with any previous therapy. Unfortunately, the treatment was apparently accompanied by serious liver damage in some cases, so that the practical application of this combination is still doubtful. It does, however, raise the hope of eventual discovery of even more effective treatments for tuberculosis than those now available.

The value of these conferences is now well established. It is therefore a matter of grave concern that financial support has not been commensurate: the conference was held only through the financial support of an anonymous donor. It would be unfortunate indeed if the continuation of this fruitful venture remained precarious. It is hoped that the Veterans Administration will include in its budget adequate provision for these conferences so that they can be properly planned and executed.

BUSMAN'S HOLIDAY

In the course of a study on coronary-artery disease among middle-aged men in different occupations in Great Britain, the observation was made that the incidence was lower among bus conductors than among bus drivers and, moreover, that the disease was less severe.[1] An interesting relation to physical

activity suggested itself, for it is evident to anyone who watches that the job of conductor on a double-decked London bus involves considerably more physical activity than that of driver. Also, among men established in the Civil Service at the same time (1949-1950), postmen had a lower incidence of coronary-artery disease, and less severe disease when they had it, than telephonists, executives and clerks with sedentary job classifications. Like the bus conductor's, the occupation of the English postman, who usually carries his mailbags on foot or on the ubiquitous bicycle, is anything but sedentary.

On the basis of this admittedly fragmentary evidence a tendency was discernible for men in physically active jobs to have "a lower incidence of coronary heart disease in middle age than have men in physically inactive jobs." Disease, when present, was not as severe in physically active as in sedentary workers, and tended to take the form of angina pectoris rather than coronary thrombosis. Ultimately, the more active workers would be expected to have "a smaller early case-fatality and a lower early mortality rate."

To test this hypothesis deaths among transport workers and postal workers in the years 1951 and 1952 within three months of an attack of coronary-artery disease were studied, and it was found that the mortality of middle-aged male workers in occupations where the work was "heavy" was half that of workers in "light" occupations.[2] Examination of a sample of death certificates from London and the Home Counties during 1952, supplemented by data supplied by the physicians who signed these certificates, indicated that workers in "heavy" industry had the disease in a more chronic form than workers in "light" industry and tended to die in later instead of in first episodes of the disease.

The "protection" against coronary-artery disease associated with physical activity at work was confirmed from different types of data, not only in particular jobs but also in jobs grouped according to a general attribute of the work involved — namely, its activity. Significance accrues from the cumulative effect of the regularities demonstrated; although the most that was established was an association rather than a causal connection, its constancy suggested a causal relation.

However, the isolation of complicating or interacting factors remains to be completed — separation of physical activity from constitution, for example, or from mental endowment and socioeconomic rewards and demands of the work performed. It is possible that emotional stresses are the opposite of physical activity, so that no matter how the data are analyzed, psychologic factors turn up along with the somatic ones on which the study was based. Nevertheless, the postulation that physical activity is related to coronary-artery disease seems reasonable enough and in no way denies the operation of important psychologic components. It is also conceivable that men who are in active jobs chose them in the first place because they were more active owing to some "constitutional" factor that accounts for the differences observed. If by "constitutional" factors hereditary or familial factors are implied — and they doubtless operate — much the same considerations apply as when psychologic factors are considered.

If the statistical evidence is accepted at face value the question arises, How could physical activity influence coronary-artery disease? There is a greater proportion of angina among the active workers, which is explicable; yet, paradoxically, active workers had a lower total incidence of coronary-artery disease. The capacity of coronary circulation demands study and possibly the protective effect on life expectancy when angina acts as a danger signal as compared with sudden thrombosis or silent atherosclerosis. The latter point raises the whole question of the relation of nutrition to atheroma and of the sequences that ensue when a heavy eater is in a job that requires little activity.

Most of the points raised should be capable of further investigation, some more easily than others. It should be possible to obtain data of physique at the time of choosing jobs. It may be possible to measure and compare coronary circulations of active and inactive workers during life and afterward to determine the degree of atheroma in men who have been subjected to different physical demands.

References

1. Morris, J. N., Heady, J. A., Raffle, P. A. B., Roberts, C. G., and Parks, J. W. Coronary heart-disease and physical activity work. I. Coronary heart-disease in different occupations. *Lancet* 2:1053-1057, 1953.
2. *Idem.* II. Statement and testing of provisional hypothesis. *Lancet* 2:1111-1120, 1953.

POSTGRADUATE MEDICAL EDUCATION

At the annual Congress on Medical Education in Chicago, the afternoon of Monday, February 8, was devoted to a discussion of postgraduate medical education. On that occasion Dr. Douglas D. Vollan gave a preview of the principal findings of the

survey of postgraduate medical education carried out by the American Medical Association. Most of the postgraduate education for physicians is didactic; 90 per cent of it is compressed into meetings less than a week in duration and held at all seasons of the year. It is for the most part offered in the large cities of the nation, and 75 per cent of the attending doctors live and practice near the points at which the education is received. It was found that the more education a doctor has received, the more he desires. The total cost of postgraduate medical education over the entire country is more than $2,000,000 per year, of which about a third is paid in the form of tuition fees by those who receive the instruction.

Dr. George N. Aagaard, chairman of the Committee on Continuation Education of the Association of American Medical Colleges, reported that those who need help most are the hardest to get help to. This is because they are the more remotely located and scattered practitioners; they tend to be isolated and to be reluctant to break away from their isolation.

Dr. Roscoe L. Pullen, dean of the University of Missouri School of Medicine, indicated the large number of variable factors determining the needs for continuation study. Each physician varies in his fundamental preparation, in the recent courses of study that he has taken, in his access to courses of instruction, in age, in environment and in the types of diseases that appear in his practice. On these accounts graduate education tends to be a highly individualized need.

Dr. U. R. Bryner, president of the American Academy of General Practice, pointed out that the primary objective is better medical care to the patient. The largest numbers of doctors who participate in postgraduate medical activities are the specialists, the next largest group being the part-time specialists and the general practitioners representing the smallest numbers. These ratios should be reversed, of course, but as yet no one knows how this can be accomplished.

It was brought out that the three-day course is the most popular; that courses in the middle of the week are best for most practitioners, especially those who live away from the center of medical education and who have to leave their home and practice for the three-day period; and that courses in the fall and winter are most popular. The number of hours reported as spent on home study and reading was surprisingly large and led to the suggestion that home-study courses might be more highly developed. A preliminary investigation of education by open-circuit television was mentioned and was considered a promising field by several of the speakers. On the other hand material being accumulated may indicate that the retention of information received by television is definitely inferior to the same information received by the so-called "live lecture."

The use of "big names in medicine" as a catalyst for speeding or increasing enrollment was said to be effective, but it was also clear that such physicians are not always the best teachers. There seemed to be a greater willingness to participate in postgraduate medical education on the part of younger men and particularly the younger men on the medical school faculties. Dr. John Conlin referred to the difficult matter of finding true leaders among a group of doctors, and described in some detail the present venture of the Postgraduate Medical Institute in Massachusetts.

Finally, if postgraduate medical education is to expand and grow more money must be invested in its development. Money is needed for traveling expenses and for the arrangement of meeting places, and to pay directors and teachers. The question of where this money should come from was discussed, but was not answered with any finality although it was generally agreed that, no matter who pays for the education, it is the consumer of medical service who is the ultimate beneficiary.

CHARLES F. WILINSKY LECTURE FUND

Among the named lectureships by means of which distinguished speakers are brought to the forums of the various universities, none bears a more honored name than the one recently established at the Harvard School of Public Health.

This is the Charles F. Wilinsky Lecture Fund, through which the leading hospital administrators of the nation — among whom Dr. Wilinsky has

been a shining example — will come to Boston "to discuss the role of the hospital in public health."

The Fund honoring the recent executive director of the Beth Israel Hospital and deputy health commissioner of Boston is the result of contributions made by Dr. Wilinsky's daughters, Mrs. Florence W. Gilbert and Mrs. Harriet W. Goodman; his son, Mr. Gene J. Wilinsky; his daughter-in-law, Mrs. Mary B. Wilinsky; his son-in-law, Mr. Sylvan A. Goodman, and his grandchildren, Joan Patricia Gilbert and Nancy Ellen Gilbert.

Surely no more fitting tribute than this could be paid to one who has devoted half a century to the public health, — although equally fitting is the selection of Dr. Wilinsky himself to deliver the first of the lectures, on April 30, on "The Relation of Hospitals and Health Departments in Tomorrow's World."

Dr. Sutherland, one of the grave-yard inspectors to the Home Office, has been seriously indisposed from inhaling poisonous gas, the escape from decaying corpses in a grave yard that he inspected. — London Lancet

Boston M. & S. J. *April 5, 1854*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

DAVID — Leo J. David, M.D., of Springfield, died on March 17. He was in his sixty-first year.

Dr. David received his degree from Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, in 1919. He was a member of the Springfield Academy of Medicine and a fellow of the American Academy of General Practice.

He is survived by his widow and son.

POLLOCK — Henry M. Pollock, M.D., of Waban, died on March 17. He was in his eighty-first year.

Dr. Pollock received his degree from University of Minnesota College of Homeopathic Medicine and Surgery in 1897. He was one of the original members of the Massachusetts Commission on Mental Diseases, and the founder and first president of the Massachusetts Hospital Association. He was professor of psychiatry, emeritus, at Boston University School of Medicine and formerly director of the Massachusetts Memorial Hospitals, a member of the New England Hospital Assembly and a fellow of the American College of Hospital Administrators.

He is survived by his widow, a son and three grandchildren.

SARGENT — George Bancroft Sargent, M.D., of Lawrence, died on February 11. He was in his eighty-fourth year.

Dr. Sargent received his degree from Harvard Medical School in 1894. He was a member of the consulting staff of the Lawrence General Hospital, corresponding secretary of Essex North District Medical Society, a councilor of the Massachusetts Medical Society, a member of the Greater Lawrence Medical Society and a fellow of the American Medical Association.

He is survived by his daughter and a brother.

WOLBACH — S. Burt Wolbach, M.D., of Sudbury, died on March 19. He was in his seventy-fourth year.

Dr. Wolbach received his degree from Harvard Medical School in 1903. He was Shattuck Professor of Pathological Anatomy, emeritus, Harvard Medical School, director of nutritional research, Children's Medical Center, consultant, Atomic Energy Commission and the United States Armed Forces Institute of Pathology, and a fellow of the National Academy of Sciences, College of American Pathologists, American Academy of Arts and Sciences, American Academy of Tropical Medicine and American Medical Association. He was a member of the American Association of Physicians, Association for Cancer Research, New England Pathological Society, Harvey Society and Societé de Pathologie Exotique and was formerly president of the American Association of Pathologists and Bacteriologists and the American Society for Experimental Pathology.

He is survived by his widow and two sons.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

RHEUMATIC-FEVER FELLOWSHIP

A fellowship in rheumatic fever is offered by the United States Children's Bureau through the Massachusetts Department of Health and Harvard Medical School. The grant will probably begin on July 1, for a year, at the House of the Good Samaritan, Children's Medical Center, Boston. Trainees should be interested in limiting their work to the fields of public health and teaching. Further information may be obtained from Dr. Benedict F. Massell, House of the Good Samaritan, 25 Binney Street, Boston 15, Massachusetts.

CORRESPONDENCE

REVOCATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held September 12, 1946, it was voted to revoke the registration of Dr. Louis A. Kotarski, formerly of 80 Washington Square, Salem, Massachusetts, because of ill health.

ROBERT C. COCHRANE, M.D.
Secretary

State House
Boston

BOOK RECEIVED

The receipt of the following book is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Electrical Methods of Blood-Pressure Recording. By Frank W. Noble, M.E.E., National Heart Institute, National Institutes of Health, Public Health Service, Federal Security Agency, Bethesda, Maryland. 8°, cloth, 56 pp., with 12 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $3.00. (Publication No. 155, *American Lecture Series.*)

The author discusses the hydraulic and electric systems that have been used in the diaphragm type of manometer. There is a bibliography and an index.

NOTICES

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the Robert Breck Brigham Hospital, Boston, on April 20 at 12 noon. The topic of discussion will be "Arthritis," and the speakers will be Drs. Robert E. Barkin, J. Sydney Stillman, Theodore A. Potter and Theodore B. Bayles.

MASSACHUSETTS HEART ASSOCIATION KIDNEY SECTION

The first professional meeting of the Kidney Section of the Massachusetts Heart Association will be held in Sprague Hall, Boston Medical Library, 8 Fenway, Boston, on April 26 at 8 p.m. The subject of the meeting will be "Practical Aspects of Renal Disease," and the program is as follows:

The Relation of Streptococcal Infections to the Development of Acute Glomerulonephritis. Dr. Louis Weinstein, Massachusetts Memorial Hospitals.

The Inter-relation of Pregnancy and Renal Disease. Dr. Duncan E. Reid, Boston Lying-in Hospital.

The Differential Diagnosis of Hematuria. Dr. Wyland F. Leadbetter, New England Center Hospital.

Kidney Diseases and Hypertension. Dr. Robert W. Wilkins, Massachusetts Memorial Hospitals.

The Management of Acute Renal Insufficiency. Dr. John P. Merrill, Peter Bent Brigham Hospital.

MASSACHUSETTS SOCIETY OF EXAMINING PHYSICIANS

The annual meeting of the Massachusetts Society of Examining Physicians will be held at the Harvard Club, Boston, on April 28 at 6 p.m. After dinner Dr. Frank G. Dickinson, director, Bureau of Economic Research of the American Medical Association, will speak on the topic "Social Security for the Physician." All physicians are invited.

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

The annual meeting of the Middlesex South District Medical Society will be held at the Hotel Continental, Cambridge, on April 28 at 6:30 p.m. After dinner Dr. Dwight E. Harken, will speak on the topic "Heart Surgery and New Responsibilities for the Physician."

TUFTS MEDICAL ALUMNI AMA DINNER

The Tufts Medical Alumni will hold an American Medical Association dinner at John's Famous Grill, 63 Ellis Street, San Francisco, on June 23 at 8 p.m. Reservations should be mailed early, accompanied by a check for $6, to Dr. M. Coleman Harris, 450 Sutter Street, San Francisco, California.

NEW YORK STATE SURGICAL DIVISION OF INTERNATIONAL COLLEGE OF SURGEONS

The northeastern sectional meeting of the New York State Surgical Division of the United States section of the International College of Surgeons will be sponsored by St. Francis Hospital, Poughkeepsie, New York, on May 27 and 28. Dr. Max M. Simon will be general chairman. Among the speakers at the surgical forum will be Drs. Max Thorek and Arnold S. Jackson.

YALE UNIVERSITY SILLIMAN LECTURES

Professor Ragnar Granit, director, Medicinska Nobelinstitutet, Neurofysiologiska Avdelningen, Stockholm, will deliver the Silliman Lectures at Yale University, April 29 and 30 and May 3, 4, 5, 6 and 7. The theme will be "Receptors and Sensory Perception," and the titles are as follows:

Historical background: The electrophysiological approach to primary processes.

Principles of Organization in Skin Organs and Retina. Fibre Size. Receptive Fields. Receptors Re-represented in the Brain.

Spontaneous Activity in Sense Organs and Its Functional Significance.

Present State of Dominator-Modulator Theory. Photochemical Correlations.

Muscle Receptors and their Reflex Action.

Spinal and Supraspinal Control of Posture and Movement by the γ-loop to the Muscle Receptors.

Sensory Discrimination and Integration.

The lectures are open to all interested persons. This year marks the fiftieth anniversary of the series.

AMERICAN COLLEGE OF CARDIOLOGY

The third annual convention of the American College of Cardiology will be held at the Conrad Hilton Hotel, Chicago, May 27–29. The theme of the meeting will be "Prognosis of Heart Disease." Further information may be obtained from Dr. Philip Reichert, 140 West 57th Street, New York 19, New York.

NATIONAL FOUNDATION FOR INFANTILE PARALYSIS FELLOWSHIPS

A limited number of fellowships will be awarded by the National Foundation for Infantile Paralysis to social scientists (either professional or predoctorate) interested in the emotional, psychologic and social factors related to the rehabilitation of physically handicapped persons. Candidates will be selected on a competitive basis and must intend to continue in the same specialty after completion of the fellowship. Applicants interested in respiratory problems will receive special consideration. Further information may be obtained from the Division of Professional Education, National Foundation for Infantile Paralysis, 120 Broadway, New York 5, New York.

NATIONAL INSTITUTE OF MENTAL-HEALTH GRANTS

The National Institute of Mental Health of the United States Public Health Service announces grants available to non-federal scientists for research and methodology, as well as grants to universities and other training centers for expanding and developing training programs for and offering traineeships to psychiatrists, psychiatric nurses, psychiatric social workers, clinical psychologists and, as a recent addition, mental-health personnel in public health. Research fellowships are now awarded to postdoctorate investigators only, and are available to workers in the fields of biochemistry, neurophysiology, psychiatry, psychology and sociology.

Applications for traineeships should be addressed to the institution of choice. Lists of these institutions are published by the Public Health Service. The pamphlet, *Training and Research Opportunities under the National Mental Health Act*, may be obtained without charge from the National Institute of Mental Health, Bethesda 14, Maryland, and if choice of specialty is indicated a list of universities and training centers awarding Public Health Service traineeships in that profession will be enclosed.

SOCIETY MEETINGS AND CONFERENCES

APRIL 5–28. Consultation Clinics for Crippled Children. Page 490, issue of March 18.

APRIL 5 and 19. Hartford Medical Society. Page 1130, issue of December 31.

APRIL 7. Massachusetts Academy of General Practice. Page 443, issue of March 11.

APRIL 8–11. International Academy of Proctology. Page 130, issue of January 21.

APRIL 8 and 20. Boston City Hospital House Officers' Association. Page 265, issue of February 11.

APRIL 9. New England Society of Anesthesiologists. Page 399, issue of March 4.

APRIL 9–MAY 21. Boston Lying-in Hospital Journal Club. Page 38, issue of January 7.

APRIL 10. American Congress of Physical Medicine. Page 266, issue of February 11.

APRIL 13. New York Society for Circulatory Diseases. Page 491, issue of March 18.

APRIL 13. Harvard Medical Society. Page 539, issue of March 25.

APRIL 17 and MAY 15. Massachusetts Hospital School. Orthopedic Rounds. Page 265, issue of February 11.

APRIL 20. South End Medical Club. Notice above.

APRIL 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

APRIL 21–24. Seminar and Conference on Cancer Cytology. Page 346, issue of February 25.

APRIL 24. Boston City Hospital Alumni Association. Page 491, issue of March 18.

APRIL 24. Massachusetts Association of Medical Technologists. Page 540, issue of March 25.

April 26. Massachusetts Heart Association. Kidney Section. Page 585.

April 26–May 2. International College of Surgeons. Page 492, issue of March 18.

April 28. Massachusetts Society of Examining Physicians. Page 585.

April 28. Middlesex South District Medical Society. Page 585.

April 29 and 30. New York Academy of Medicine. Eastern States Health-Education Conference. Page 491, issue of March 18.

April 29, 30 and May 1. American Goiter Association. Hotel Somerset, Boston.

April 29 and 30 and May 3–7. Yale University Silliman Lectures. Page 585.

May 1. State University College of Medicine at New York City. Alumni Association. Page 400, issue of March 4.

May 10–12. Institute of Industrial Health. Page 491, issue of March 18.

May 11. Middlesex East District Medical Society. Annual Meeting. (Harlow Dinner.)

May 12. Essex North District Medical Society Meeting. Andover Country Club, Andover.

May 12. New England Obstetrical and Gynecological Society. Spring Meeting. Longmeadow Country Club, Springfield.

May 14–16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

May 14–16. American Academy of Dental Medicine. Page 38, issue of January 7.

May 27 and 28. New York Surgical Division of International College of Surgeons. Page 585.

May 27–29. American College of Cardiology. Page 585.

May 31–June 3. American Urological Association. Page xvii, issue of July 23.

June 5 and 6. International Association for the Study of the Bronchi. Page 400, issue of March 4.

June 13–17. American Society of Medical Technologists. Page 444, issue of March 11.

June 14–16. American Neurological Association. Page 540, issue of March 25.

June 15–18. Medical Library Association. Page 491, issue of March 18.

June 17–19. American Geriatrics Society. Page 266, issue of February 11.

June 17–21. Pan American Congress of Ophthalmology. Page 540, issue of March 25.

June 19 and 20. Society for Investigative Dermatology. Page 540, issue of March 25.

June 23. Tufts Medical Alumni AMA Dinner. Page 585.

July 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

July 23–29. International Cancer Congress. Page 914, issue of November 26.

July 26–31. International Congress of Gynecology and Obstetrics. Page 400, issue of March 4.

September 6–10. International Poliomyelitis Congress. Page 399, issue of March 4.

September 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

September 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

September 16–18. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

October 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

June 21–25, 1955. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

Calendar for the Week Beginning Thursday, April 8

Thursday, April 8

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m. Psychiatric Conference. Dr. Wilfred Bloomberg. Regional Office of the Veterans Administration. Conference Room, 4th floor, 17 Court Street, Boston.

11:00 a.m. Thoracic Conference. Cardiac Resuscitation. Drs. William Bernhardt and Juro Wada. Discussion by Mr. E. Lloyd Claff, Drs. Dwight E. Harken, Harrison Black and William Derrick. Main Amphitheater, Peter Bent Brigham Hospital.

*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.–1:00 p.m. The Abnormality of Calcium Metabolism in Sarcoid. Dr. Philip H. Henneman. Stearns Auditorium, New England Center Hospital.

2:00 p.m. New England Society of Psychiatry. A Psychiatric Hospital for Children, Present and Future. Dr. Thaddeus P. Brush. Wrentham State School, Wrentham.

5:00 p.m. Case Presentation and Pathological Discussion, Followed by a Subject of Special Presentation. Joslin Amphitheater, New England Deaconess Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

8:30 p.m. Pentucket Association of Physicians. Management of Abdominal Injuries. Dr. Grant V. Rodkey. Diburro's Restaurant, corner of Wingate and Essex streets, Haverhill.

Friday, April 9

*8:00 a.m.–9:00 p.m. New England Society of Anesthesiologists. Hotel Beaconsfield, 1731 Beacon Street, Brookline.

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

4:00 p.m. Boston Lying-in Hospital Journal Club. Anemias in Pregnancy. Dr. Maurice B. Strauss. Boston Lying-in Hospital Auditorium, 221 Longwood Avenue.

*4:00–6:00 p.m. X-Ray Conference. Dr. Richard Schatzki. Stearns Auditorium, New England Center Hospital.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

7:00 p.m. House Officers' Association of the Boston City Hospital. Dr. Leon Schiff. Dowling Amphitheater, Boston City Hospital.

Saturday, April 10

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Diagnostic Clinic. New England Center Hospital.

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*10:30–11:00 a.m. Surgical History Meeting. Stearns Auditorium, New England Center Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Auditorium, New England Center Hospital.

Monday, April 12

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Foot Problems. New England Deaconess Hospital.

*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater. Dowling Building, Boston City Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:00 m.–1:00 p.m. Medical Clinic. Dr. Thannhauser. Stearns Auditorium, New England Center Hospital.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

4:00–5:00 p.m. Surgical Pathology Conference. Discussed by Dr. H. E. MacMahon. Stearns Auditorium, New England Center Hospital.

7:00–9:00 p.m. Combined Anesthesia Resident Training Program. Jimmy Fund Building. Children's Medical Center, 35 Binney Street.

Tuesday, April 13

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m. X-Ray Conference. Drs. Harry Goldman and Boris Bushueff. Regional Office of the Veterans Administration. Conference Room, 4th floor, 17 Court Street, Boston.

*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building, Boston City Hospital.

*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.

*12:30–1:30 p.m. Medical Journal Club. Cafeteria. New England Deaconess Hospital.

*4:00–5:30 p.m. Anesthesia Teaching Conference. Dr. Etsten. Stearns Auditorium, New England Center Hospital.

*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.

*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

(Notices concluded on page xvi)